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(71) Applicant *(for all designated States except US)*: **MOUNT SINAI HOSPITAL** [CA/CA]; 600 University Avenue, Toronto, Ontario M5G 1X5 (CA).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **SICHERI, Frank** [CA/CA]; Apartment 2110, 77 Gerard Street, Toronto, Ontario M5G 2A1 (CA). **WYBENGA-GROOT, Leanne** [CA/CA]; 7 Gem Place, Etobicoke, Ontario M9W 2P4 (CA). **PAWSON, Tony** [GB/CA]; 34 Glenwood Avenue, Toronto, Ontario M6P 3C6 (CA).

(74) Agent: **BERESKIN & PARR**; 40 King Street West, 40th Floor, Toronto, Ontario M5H 3Y2 (CA).

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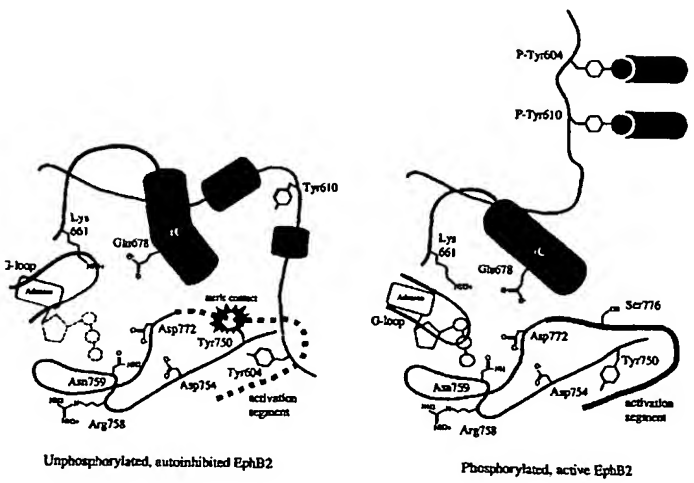
(54) Title: COMPOSITIONS AND METHODS FOR REGULATING THE KINASE DOMAIN OF RECEPTOR TYROSINE KINASES



Unphosphorylated, autoinhibited EphB2

Phosphorylated, active EphB2

(57) Abstract: The present invention relates to binding pockets of receptor tyrosine kinases (RTKs). The binding pockets may regulate the kinase domain of the receptor tyrosine kinases. In particular, the invention relates to a crystal comprising a binding pocket of a receptor tyrosine kinase that regulates the kinase domain of the receptor tyrosine kinase. The crystal may be useful for modeling and/or synthesizing mimetics of a binding pocket or ligands that associate with the binding pocket. Such mimetics or ligands may be capable of acting as modulators of receptor tyrosine kinase receptor activity, and they may be useful for treating, inhibiting, or preventing diseases modulated by such receptors. Methods are also provided for regulating the kinase domain of an RTK by changing a binding pocket of the RTK that regulates the kinase domain from an autoinhibited state to an active state or from an active state to an autoinhibited state.

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Title: Compositions and Methods for Regulating the Kinase Domain of Receptor Tyrosine Kinases

FIELD OF THE INVENTION

The present invention relates to binding pockets of receptor tyrosine kinases (RTKs). The binding pockets may regulate the kinase domain of the receptor tyrosine kinases. In particular, the invention relates to a crystal comprising a binding pocket of a receptor tyrosine kinase that regulates the kinase domain of the receptor tyrosine kinase. The crystal may be useful for modeling and/or synthesizing mimetics of a binding pocket or ligands that associate with the binding pocket. Such mimetics or ligands may be capable of acting as modulators of receptor tyrosine kinase receptor activity, and they may be useful for treating, inhibiting, or preventing diseases modulated by such receptors.

Methods are also provided for regulating the kinase domain of an RTK by changing a binding pocket of the RTK that regulates the kinase domain from an autoinhibited state to an active state or from an active state to an autoinhibited state.

BACKGROUND

Cell surface receptors with protein-tyrosine kinase activity mediate the biological effects of many extracellular signaling proteins, and thereby regulate aspects of normal cellular behavior such as growth and differentiation, movement, metabolism and survival (van der Geer and Hunter, 1994). The profound consequences of phosphotyrosine signaling on cellular function are emphasized by the effects of mutations that deregulate receptor tyrosine kinase activity, which are frequently associated with malignant transformation or developmental abnormalities. Under normal circumstances, the activation of receptor tyrosine kinases (RTK) requires binding of the appropriate extracellular ligand, which induces either receptor oligomerization or a spatial re-organization of pre-associated receptor chains (Heldin, 1995; Remy et al., 1999; Schlessinger, 2000). As a result, the receptor undergoes autophosphorylation through an intermolecular reaction, both on tyrosine residues which regulate kinase activity, and on residues within non-catalytic regions of the receptor which form binding sites for cytoplasmic targets with SH2 or PTB domains (Pawson and Scott, 1997; Kuriyan and Cowburn, 1997).

The catalytic activity of tyrosine kinases is frequently stimulated by autophosphorylation within a region of the kinase domain termed the activation segment (Weinnmaster et al., 1984), and indeed this has been viewed as the principal mechanism through which RTKs are activated (Hubbard and Till, 2000; Hubbard, 1997). Structural analysis of the isolated kinase domains of several receptors has revealed how the activation segment represses kinase activity, and the means by which phosphorylation releases this autoinhibition. In the case of the inactive insulin receptor, Tyr 1162 in the activation segment protrudes into the active site, and the activation segment blocks access to the ATP-binding site (Hubbard et al., 1994). Autophosphorylation of Tyr 1162 and two adjacent tyrosine residues repositions the activation segment, thereby freeing the active site to engage exogenous substrates and reorganizing the residues

required for catalysis into a functional conformation (Hubbard, 1997). In contrast, the activation segment of the fibroblast growth factor (FGF) receptor is relatively mobile and the tyrosines which become phosphorylated upon receptor activation do not occupy the active site. However, the C-terminal end of the FGFR1 activation segment appears to block access to substrate (Mohammadi et al., 1996).

Despite the evident importance of the kinase domain activation segment, it remains possible that other mechanisms are important in regulating RTK activity, which might have been missed through an exclusive focus on the kinase domain itself. In particular, recent biochemical and mutational analysis has suggested that Eph receptors may be regulated through a more complex mechanism, involving the juxtamembrane region (Binns et al., 2000; Zisch et al., 1998; Zisch et al., 2000).

There is only a single Eph receptor tyrosine kinase encoded by the *C. elegans* genome (VAB-1) (George et al., 1998; Wang et al., 1999a), but the subfamily has undergone a remarkable expansion during metazoan evolution to include at least 14 mammalian members, which therefore represent the largest class of vertebrate RTKs (Holder and Klein, 1999). These Eph receptors fall into two groups, A and B, based on their ability to bind ligands (ephrins), which are themselves cell surface proteins anchored to the plasma membrane either through a GPI linkage (A-type ephrins) or a transmembrane region (B-type) (Eph Nomenclature Committee, 1997; Gale et al., 1996). Signaling between Eph receptors and ephrins generally involves direct cell-cell interactions (Holland et al., 1996; Bruckner et al., 1997), and frequently results in the repulsion of these cells one from another (Drescher et al., 1995; Wang and Anderson, 1997; Mellitzer et al., 1999). Eph receptors are implicated in morphogenetic cell movements (Wang et al., 1999a; Chin-Sang et al., 1999), in defining cell boundaries in structures such as the rhombomeres of the embryonic hindbrain (Xu et al., 1999), in controlling axon guidance and the establishment of topographic maps in the central nervous system (Nakamoto et al., 1996; Brown et al., 2000), and in determining the trajectories of migrating neural crest cells (Krull et al., 1997). Signaling between ephrin and Eph receptor-expressing cells is also essential for angiogenesis, and in conferring distinct arterial and venous identities to developing blood vessels (Wang et al., 1999b; Adams et al., 1999; Gerety et al., 1999).

The extracellular region of Eph receptors contains an N-terminal ephrin-binding domain (Labrador et al., 1997), that folds into a jellyroll β-sandwich (Himanen et al., 1998), followed by a cysteine-rich region and two fibronectin type III repeats (Pasquale, 1991; Henkemeyer et al., 1994). A single membrane-spanning sequence is followed by a relatively lengthy juxtamembrane region, an uninterrupted kinase domain, an α-helical sterile alpha motif (SAM) domain implicated in receptor oligomerization (Stapleton et al., 1999; Thanos et al., 1999), and a C-terminal motif capable of binding PDZ domain proteins (Hock et al., 1998; Torres et al., 1998) . Activation of receptors such as EphB2 or EphA4 is accompanied by autophosphorylation on multiple residues, most notably on two tyrosines within a highly conserved juxtamembrane motif (YIDPFTYEDP in EphB2) and on a tyrosine within the activation segment of the kinase domain (Holland et al., 1997; Choi and Park, 1999; Ellis et al., 1996; Kalo and Pasquale, 1999; Zisch et al., 1998; Binns et al., 2000). By analogy with other RTKs, it might be expected that autophosphorylation of the activation segment tyrosine would stimulate kinase activity, while the juxtamembrane phosphotyrosine sites would recruit cytoplasmic targets. Indeed, the

juxtamembrane phosphotyrosine motifs do bind SH2 domain signaling proteins, including p120-RasGAP, Nck, phosphatidylinositol 3'-kinase, SHEP-1 and Src family kinases among others, which can potentially direct cellular responses to ephrin stimulation (Dodelet et al., 1999; Ellis et al., 1996; Holland et al., 1997; Holland et al., 1998; Zisch et al., 1998).

Consistent with the possibility that phosphorylation of the conserved juxtamembrane tyrosines is important for signaling, substitution of these residues in EphB2 with phenylalanine abrogates EphB2-mediated growth cone collapse upon stimulation of NG108 neuronal cells with ephrin B1. However, this loss of biological activity is apparently not due solely to a failure to engage SH2-containing targets, since substitution of the juxtamembrane tyrosines in EphB2 and EphA4 with phenylalanine leads to a severe loss of ephrin-induced kinase activity (Binns et al., 2000).

SUMMARY OF THE INVENTION

Applicants have solved the x-ray crystal structure of an Eph receptor tyrosine kinase domain and juxtamembrane region in an autoinhibited state. The results show that in its unphosphorylated state, the juxtamembrane region adopts a helical structure that distorts the conformation of the small lobe of the kinase domain, thereby disrupting the active site. These results indicate a novel mechanism for the regulation of RTKs.

Solving the crystal structure has enabled the determination of key structural features of the kinase domain and juxtamembrane region, particularly the shape of binding pockets, or parts thereof, that permit the juxtamembrane region and kinase domain to associate resulting in an autoinhibited state. The crystal structure has also enabled the determination of key structural features in molecules or ligands that interact or associate (e.g. nucleotides, cofactors, inhibitors, and substrates) with the binding pockets.

Knowledge of the autoinhibited conformation of binding pockets of RTKs that regulate the kinase domain is of significant utility in drug discovery. The association of natural ligands and substrates with the binding pockets of RTKs is the basis of many biological mechanisms. In addition, many drugs exert their effects through association with the binding pockets of RTKs. The associations may occur with all or any parts of a binding pocket. An understanding of the association of a drug with the active and autoinhibited conformations of binding pockets of RTKs, will lead to the design and optimization of drugs having more favorable associations with their target RTKs and thus provide improved biological effects. Therefore, information about the shape and structure of binding pockets of RTKs in their autoinhibited and activated states, is invaluable in designing potential modulators of the receptors for use in treating diseases and conditions associated with or modulated by the receptors.

The present invention relates to a binding pocket of a receptor tyrosine kinase (RTK). In an aspect of the invention, the binding pocket regulates the kinase domain of the receptor tyrosine kinase or is involved in maintaining an autoinhibited state or active state of an RTK.

The invention also relates to a crystal comprising a binding pocket of an RTK that regulates the kinase domain of the RTK. The binding pocket may be in an autoinhibited state, or active state. Thus, a binding pocket may be involved in maintaining an autoinhibited state or active state of an RTK.

In an embodiment, the invention, provides a crystal comprising a juxtamembrane region and/or kinase domain of an RTK, or part thereof. The invention contemplates a crystal formed by a juxtamembrane region and a kinase domain of an RTK in an autoinhibited state or active state.

The invention also contemplates a crystal comprising a binding pocket of a receptor tyrosine kinase that regulates the kinase domain of the receptor tyrosine kinase in association with a ligand.

The present invention also contemplates molecules or molecular complexes that comprise all or parts of either one or more binding pockets of the invention, or homologs of these binding pockets that have similar structure and shape.

The present invention also provides a crystal comprising a binding pocket of an RTK of the invention and at least one ligand. A ligand may be complexed or associated with a binding pocket. Ligands include a nucleotide or analogue or part thereof, a substrate or analogue thereof, a cofactor, and/or heavy metal atom. A ligand may be a modulator of the activity of an RTK.

In an aspect the invention contemplates a crystal comprising a binding pocket of an RTK of the invention complexed with a nucleotide or analogue thereof from which it is possible to derive structural data for the nucleotide or analogue thereof.

The shape and structure of a binding pocket may be defined by selected atomic contacts in the pocket. In an embodiment, the binding pocket is defined by one or more atomic interactions or enzyme atomic contacts as set forth in Table 2. Each of the atomic interactions is defined in Table 2 by an atomic contact (more preferably, a specific atom where indicated) on the juxtamembrane region and by an atomic contact (more preferably a specific atom where indicated) on the kinase domain, juxtamembrane region, or ligand.

An isolated polypeptide comprising a binding pocket with the shape and structure of a binding pocket described herein is also within the scope of the invention.

The invention also provides a method for preparing a crystal of the invention, preferably a crystal of a binding pocket of an Eph receptor, or a complex of such a binding pocket and a ligand.

Crystal structures of the invention enable a model to be produced for a binding pocket of the invention, or complexes or parts thereof. The models will provide structural information about the autoinhibited or active state of a binding pocket of a RTK or a ligand and its interactions with a binding pocket. Models may also be produced for ligands. A model and/or the crystal structure of the present invention may be stored on a computer-readable medium.

The present invention includes a model of a binding pocket of the present invention that substantially represents the structural coordinates specified in Table 3. The invention also includes a model that comprises modifications of the model substantially represented by the structural coordinates specified in Table 3. A modification may represent a binding pocket that is involved in maintaining an autoinhibited state or active state of an RTK or regulates the kinase domain of an RTK. A model is a representation or image that predicts the actual structure of the binding pocket. As such, a model is a tool that can be used to probe the relationship between a binding pocket's structure and function at the atomic level, and to design molecules that can modulate the binding site and accordingly RTK activity.

Thus, the invention provides a model of: (a) a binding pocket of an RTK that is involved in maintaining an autoinhibited state or active state of an RTK or regulates the kinase domain of an RTK; and (b) a modification of the model of (a).

A method is also provided for producing a model of the invention representing a binding pocket of an RTK that is involved in maintaining an autoinhibited state or active state of an RTK or regulates the kinase domain of an RTK, comprising representing amino acids of the binding pocket at substantially the structural coordinates specified in Table 3.

A crystal and/or model of the invention may be used in a method of determining the secondary and/or tertiary structures of a polypeptide or binding pocket with incompletely characterised structure. Thus, a method is provided for determining at least a portion of the secondary and/or tertiary structure of molecules or molecular complexes which contain at least some structurally similar features to a binding pocket of the invention. This is achieved by using at least some of the structural coordinates set out in Table 3.

A crystal of the invention may be useful for designing, modeling, identifying, evaluating, and/or synthesizing mimetics of a binding pocket or ligands that associate with a binding pocket. Such mimetics or ligands may be capable of acting as modulators of receptor tyrosine kinase activity, and they may be useful for treating, inhibiting, or preventing diseases modulated by such receptors.

Thus, the present invention contemplates a method of identifying a modulator of an RTK comprising the step of applying the structural coordinates of a binding pocket, or atomic interactions, or atomic contacts of a binding pocket, to computationally evaluate a test ligand for its ability to associate with the binding pocket, or part thereof. Use of the structural coordinates of a binding pocket, or atomic interactions, or atomic contacts of a binding pocket to design or identify a modulator is also provided.

In an embodiment, the invention contemplates a method of identifying a modulator of an RTK comprising determining if a test agent inhibits or potentiates an autoinhibited state or active state of a kinase domain of the RTK.

The invention further contemplates classes of modulators of RTKs based on the shape and structure of a ligand defined in relation to the molecule's spatial association with a binding pocket of the invention. Generally, a method is provided for designing potential inhibitors of RTKs comprising the step of applying the structural coordinates of a ligand defined in relation to its spatial association with a binding pocket, or a part thereof, to generate a compound that is capable of associating with the binding pocket.

It will be appreciated that a modulator of an RTK may be identified by generating an actual secondary or three-dimensional model of a binding pocket, synthesizing a compound, and examining the components to find whether the required interaction occurs.

A potential modulator of an RTK identified by a method of the present invention may be confirmed as a modulator by synthesizing the compound, and testing its effect on the RTK in an assay for that receptor's enzymatic activity. Such assays are known in the art (e.g. phosphorylation assays).

A modulator of the invention may be converted using customary methods into pharmaceutical compositions. A modulator may be formulated into a pharmaceutical composition containing a modulator either alone or together with other active substances.

Therefore, the methods of the invention for identifying modulators may comprise one or more of the following additional steps:

(a) testing whether the modulator is a modulator of the activity of a RTK, preferably testing the activity of the modulator in cellular assays and animal model assays;

(b) modifying the modulator;

(c) optionally rerunning steps (a) or (b); and

(d) preparing a pharmaceutical composition comprising the modulator.

Steps (a), (b) (c) and (d) may be carried out in any order, at different points in time, and they need not be sequential.

Still another aspect of the present invention provides a method of conducting a drug discovery business comprising:

(a) providing one or more systems employing the atomic interactions, atomic contacts, or structural coordinates of a binding pocket of an RTK, for identifying agents by their ability to inhibit or potentiate the atomic interactions or atomic contacts of a binding pocket; and

(b) conducting therapeutic profiling of agents identified in step (a), or further analogs thereof, for efficacy and toxicity in animals; and

(c) formulating a pharmaceutical preparation including one or more agents identified in step (b) as having an acceptable therapeutic profile.

A further aspect of the present invention provides a method of conducting a drug discovery business comprising:

(a) providing one or more systems for identifying agents by their ability to inhibit or potentiate an autoinhibited state or active state of a kinase domain of an RTK; and

(b) conducting therapeutic profiling of agents identified in step (a), or further analogs thereof, for efficacy and toxicity in animals; and

(c) formulating a pharmaceutical preparation including one or more agents identified in step (b) as having an acceptable therapeutic profile.

In certain embodiments, the subject methods can also include a step of establishing a distribution system for distributing the pharmaceutical preparation for sale, and may optionally include establishing a sales group for marketing the pharmaceutical preparation.

Yet another aspect of the invention provides a method of conducting a target discovery business comprising:

(a) providing one or more systems employing the atomic interactions, atomic contacts, or structural coordinates of a binding pocket of an RTK, for identifying agents by their ability to inhibit or potentiate the atomic interactions or atomic contacts, or providing one or more

systems for identifying agents by their ability to inhibit or potentiate an autoinhibited state or active state of a kinase domain of an RTK;

(b) (optionally) conducting therapeutic profiling of agents identified in step (a) for efficacy and toxicity in animals; and

(c) licensing, to a third party, the rights for further drug development and/or sales for agents identified in step (a), or analogs thereof.

Methods are also provided for regulating the kinase domain of an RTK by changing a binding domain or pocket of a RTK that regulates the kinase domain from an autoinhibited state to an active state or from an active state to an autoinhibited state. A binding domain or pocket of a RTK may be changed from an autoinhibited state by altering amino acid residues forming the binding pocket (e.g. introducing mutations) or using a modulator.

In an aspect the invention provides a method for inhibiting kinase activity of an RTK comprising maintaining the RTK or a binding pocket thereof involved in regulating the kinase domain in an autoinhibited state, or potentiating an autoinhibited state for the RTK or binding pocket thereof involved in regulating the kinase domain. An autoinhibited state may be maintained or potentiated by inhibiting phosphorylation of phosphoregulatory sites of the juxtamembrane segment and/or kinase domain (e.g. activation segment). Inhibition may be accomplished using modulators, or altering the structure of a binding pocket of the RTK comprising the phosphoregulatory sites, to prevent phosphorylation of the sites.

The invention contemplates a method for altering the stability of an autoinhibited state of an RTK comprising phosphorylating phosphoregulatory sites of a juxtamembrane region of the RTK.

In an aspect the invention relates to a method for changing an RTK from an autoinhibited state to an active state comprising phosphorylating phosphoregulatory sites of a juxtamembrane region of the RTK.

In another aspect the invention provides a method for activating kinase activity of an RTK comprising phosphorylating phosphoregulatory sites of a juxtamembrane region and kinase domain (e.g. activation segment) of the RTK involved in maintaining the RTK in an autoinhibited state.

The invention also contemplates a method of treating or preventing a condition or disease associated with an RTK in a cellular organism, comprising:

(a) administering a modulator of the invention in an acceptable pharmaceutical preparation; and

(b) activating or inhibiting the RTK to treat or prevent the disease.

In an aspect the invention provides a method for treating or preventing a condition or disease involving increased RTK activity comprising maintaining the RTK or a binding pocket thereof involved in regulating the kinase domain of the RTK in an autoinhibited state. An autoinhibited state may be maintained as described herein. In an embodiment the condition or disease is cancer.

The invention provides for the use of a modulator identified by the methods of the invention in the preparation of a medicament to treat or prevent a disease in a cellular organism. Use of modulators of the invention to manufacture a medicament is also provided.

These and other aspects of the present invention will become evident upon reference to the following detailed description and Tables, and attached drawings.

DESCRIPTION OF THE DRAWINGS AND TABLES

The present invention will now be described only by way of example, in which reference will be made to the following Figures:

Figure 1. Structure-based sequence alignment of the juxtamembrane segments and kinase domains of murine and human EphB2, murine EphA4 and cAPK, and human IRK, FGFR1, Hck, Kit, PDGFRβ, and Flt3. The secondary structure elements of murine EphB2 are indicated, with the juxtamembrane segment, the N-terminal kinase, the g-loop, and the C-terminal lobe coloured red, green, orange, and blue, respectively. Residues Phe 620 and Tyr 750 and those marked with a star are involved in the juxtamembrane/kinase domain interface. The two juxtamembrane tyrosines (604 and 610) that were mutated to phenylalanine are highlighted in light blue. Additional tyrosines identified by Kalo and Pasquale (1999) as *in vivo* phosphorylation sites are highlighted in purple. The solid triangle indicates the site of a 16 amino acid insertion in chicken EphB2 resulting from alternate RNA processing (Connor and Pasquale, 1995). For Kit and PDGFRβ, tyrosines highlighted in yellow denote autophosphorylation sites, while sites of activating point mutations and deletions are shaded gray (Tsujimura et al., 1996; Irusta and DiMaio, 1998; Kitayama et al., 1995; Hirota et al., 1998). The locations and regions of duplicated sequence for activating Flt3 mutations are indicated by solid black triangles and underlining (Hayakawa et al, 2000).

Figure 2. Overview of the autoinhibited EphB2 structure. (a) Ribbon diagram of the EphB2 crystal structure in complex with AMP-PNP. The juxtamembrane region, N-terminal kinase lobe, C-terminal kinase lobe, and g-loop are coloured red, green, blue and orange, respectively. Phosphoregulatory residues Tyr/Phe 604 and Tyr/Phe 610 are coloured light blue, Tyr667 is coloured purple, and the adenine moiety of AMP-PNP is coloured red. (b) Ribbon representation of EphB2 colored as in (a), rotated 90° about the vertical axis. (c) and (d) The juxtamembrane regions in (a) and (b), respectively, have been magnified to detail the interactions between the juxtamembrane region and helix αC of the N-terminal kinase lobe. Carbon, oxygen, nitrogen and sulfur atoms are shown in yellow, red, blue, and green, respectively. Residues involved in the juxtamembrane/kinase domain interface but not shown include Ala616, Ala621, Leu676, Leu693, and Val696. All ribbon diagrams were prepared with RIBBONS (Carson, 1991b).

Figure 3. Comparison of autoinhibited EphB2 RTK with the active insulin receptor kinase. (a) Superposition of EphB2 with active insulin receptor kinase (Protein Data Bank ID code 1ir3). The backbone of the juxtamembrane region of EphB2 is shown in red, with the side chains of Tyr/Phe 604 and Tyr/Phe 610 coloured light blue. The EphB2 kinase domain, g-loop and bound adenine moiety are colored blue, orange and red, respectively. The backbone of active IRK is coloured dark green with its activation segment, g loop, and bound nucleotide shown in purple, pink, and light green respectively. The two receptors were aligned using all elements of the C-terminal lobes except the kinase insert region, the activation segment, helix αJ, and the C-terminal tail (rms fit = 1.91 Å). (b) Stereo view of the boxed

region in (a), with EphB2 phosphorylation sites shown in purple, other EphB2 side chain atoms coloured as in Figure 2c and 2d and IRK side chains shown in green and pink. (c) Stereo view of the boxed region in A), highlighting the kinase catalytic region. This panel is colored as in (b). (d) Stereo view of boxed region in A) highlighting switch region 1. Inactive IRK (Protein Data Band ID code 1irk), shown in yellow, is also superimposed. All side chains are colored according to their respective backbones. IRK residue labeled Thr776 corresponds to Ser776 in EphB2.

Figure 4. Electrostatic surface representation of EphB2. Blue and red regions indicate positive and negative potential, respectively (10 to -10 k_BT). Phosphoregulatory residues Tyr/Phe 604 and Tyr/Phe 610 are coloured light blue. The molecular surface of EphB2 is oriented as in Figure 2a and was generated using GRASP (Nicholls et al., 1991)

Figure 5. Comparison of the kinase activities of EphA4 and EphB2 wild-type and mutant proteins. (a) GST-EphA4 proteins were expressed in E.coli, and cell lysates were subjected to immunoblot analysis with anti-pTyr antibody (top panel) and anti-GST antibody (lower panel). (b) Equal quantities of GST-EphA4 proteins bound to glutathione sepharose were assessed for their ability to autophosphorylate and phosphorylate enolase by an in vitro kinase assay (top panel). Immunblot analysis of GST-EphA4 proteins with anti-GST antibody (lower panel). (c) Histogram of the specific activities of EphA4 wild-type and mutant proteins as measured by the spectrophotometric coupling assay at 1 mM S-1 peptide and 0.5μM EphA4 proteins. The velocities represent the mean of triplicate reactions and have been normalized to the specific activity of wild-type EphA4 (top panel). Coomassie stained SDS-PAGE analysis of EphA4 proteins (lower panel). (d) EphB2 and its mutants were expressed in COS-1 cells and immunoprecipitated. The immunoprecipitates were resolved by SDS-PAGE, immunoblotted with anti-pTyr (top panel) or anti-EphB2 (middle panel) antibodies, and assessed for their ability to autophosphorylate and phosphorylate enolase by an in vitro kinase assay (bottom panel).

Figure 6. Schematic diagram highlighting differences between the autoinhibited (left) and active (right) states of the Eph receptor family of tyrosine kinases. The active configuration is based on the crystal structure of active IRK (Protein Data Bank ID code 1ir3). Dashed lines indicate regions of activation segment disorder. The numbering scheme corresponds to murine EphB2.

The present invention will now be described only by way of example, in which reference will be made to the following Tables:

Table 1 shows the data collection, structure determination and refinement statistics

Table 2 shows intermolecular contacts in a binding pocket of the invention.

Table 3 shows the structural coordinates of the juxtamembrane region and kinase domain of an EphB2 receptor.

In Table 3, from the left, the second column identifies the atom number; the third identifies the atom type; the fourth identifies the amino acid type; the sixth identifies the residue number; the seventh identifies the x coordinates; the eighth identifies the y coordinates; the ninth identifies the z coordinates; the tenth identifies the occupancy; and the eleventh identifies the temperature factor.

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise indicated, all terms used herein have the same meaning as they would to one skilled in the art of the present invention. Practitioners are particularly directed to Current Protocols in Molecular Biology (Ansubel) for definitions and terms of the art.

In accordance with the present invention there may be employed conventional biochemistry, enzymology, molecular biology, crystallography, bioinformatics, microbiology, and recombinant DNA techniques within the skill of the art. Such techniques are explained fully in the literature. See for example, Sambrook, Fritsch, & Maniatis, Molecular Cloning: A Laboratory Manual, Second Edition (1989) Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y); DNA Cloning: A Practical Approach, Volumes I and II (D.N. Glover ed. 1985); Oligonucleotide Synthesis (M..J. Gait ed. 1984); Nucleic Acid Hybridization B.D. Hames & S.J. Higgins eds. (1985); Transcription and Translation B.D. Hames & S.J. Higgins eds (1984); Animal Cell Culture R.I. Freshney, ed. (1986); Immobilized Cells and enzymes IRL Press, (1986); and B. Perbal, A Practical Guide to Molecular Cloning (1984).

For ease of reference the murine numbering scheme for EphB2 is employed herein to describe specific amino acid residues in aspects of the invention. However, a person skilled in the art could readily determine the corresponding amino acid residues in other RTKs, more particularly in Eph receptors.

Receptor Tyrosine Kinases (RTKs)

The invention generally relates to RTKs. RTKs mediate pathways involving multiple extracellular and intracellular signals, integration and amplification of these signals by second messengers, and the activation of cellular processes including cell proliferation, cell division, cell growth, the cell cycle, cell differentiation, cell migration, axonogenesis, nerve cell interactions, and regeneration. Signaling pathways mediated by receptor tyrosine kinases may be initiated by growth factors binding to specific RTKs on cell surfaces. The binding of a growth factor to its receptor activates RTK signaling pathways. The RTKs have an extracellular N-terminal domain that binds the growth factor and a cytoplasmic C-terminal domain containing a protein tyrosine kinase that is capable of autophosphorylation, and the phosphorylation of other protein substrates. Autophosphorylation takes place within a region of the kinase domain of the RTK termed the "activation segment" (Weinnmaster et al., 1984). The binding of a growth factor to its receptor activates the tyrosine kinase which phosphorylates a variety of signaling molecules thereby initiating signaling pathways that can lead to DNA replication, RNA and protein synthesis, and cell division.

Receptor tyrosine kinases within the scope of the present invention include but are not limited to epidermal growth factor receptor (EGFR), PDGF receptor, insulin receptor tyrosine kinase (IRK), Met receptor tyrosine kinase, fibroblast growth factor (FGF) receptor, insulin receptor, insulin growth factor (IGF-1) receptor, TrkA receptor, IL-3 receptor, B cell receptor, TIE-1, Tek/Tie2, Flt-1, Flk, VEGFR3, EFGR/Erbb, Erb2/neu, Erb3, Ret, Kit, Alk, Axl, FGFR1, FGFR2, FGFR3, Hck, cAPK, keratinocyte growth factor (KGF) receptor, and Eph receptors.

The invention preferably contemplates Eph receptors, more preferably EphB2 receptors.

The term "Eph receptor" refers to a subfamily of closely related transmembrane receptor tyrosine kinases related to Eph, a receptor named for its expression in an erythropoietin-producing human

hepatocellular carcinomas cell line. The receptors contain cell adhesion-like domains on their extracellular surface. The N-terminal extracellular region of all Eph family members contains a domain necessary for ligand binding and specificity, followed by a cysteine-rich domain and two fibronectin type II repeats. The cytoplasmic region has a centrally located tyrosine kinase domain. C-terminal to the catalytic region is a sterile alpha motif (SAM) domain, which forms dimers of oligomers in solution and may contribute to regulation of receptor clustering. Localization of clustering of Eph proteins may also be influenced by PDZ domain effectors which potentially interact with specific C-terminal receptor motifs.

N-terminal to the kinase domain is the juxtamembrane domain. Two invariant tyrosine residues (tyrosines 596 and 602 of EphA4; tyrosines 604 and 610 of EphB2) in the juxtamembrane domain are embedded in a characteristic and highly conserved ~10 amino acid sequence motif. These tyrosine residues are major sites for autophosphorylation and they have been found to associate with a number of SH2 domain-containing cytoplasmic proteins such as Ras GTPase-activating protein (RasGAP), the p85 subunit of phosphatidylinositol 3' kinase, Src family kinases, the adapter protein Nck, and SHEP-1 which binds the R-Ras and Rap1A GTPases. Signaling mediated by such SH2 domain-containing proteins may contribute to the physiological effects of Eph receptor stimulation on cell adhesion and cytoskeletal structures.

There are currently 14 related vertebrate members of the Eph receptor family including receptors in *Caenorhabditis elegans* and *Drosophila*. Eph receptors are activated by ephrins. Ephrins are attached to the plasma membrane either via a glycosylphosphatidylinositol linkage (A class) or a transmembrane sequence (B class). Eph receptors are also divided into A and B classes corresponding to their ligand binding specificities and phylogenetic relationships. Class A receptors generally bind A class ephrins, whereas B class ephrins stimulate B class receptors. However, EphA4 is an exception in that it binds and responds to B as well as A class ephrins.

The group that includes receptors interacting preferentially with ephrin A proteins is called EphA and includes EphA1 (also known as Eph and Esk), EphA2 (also known as Eck, Myk2, Sek2), EphA3 (also known as Cek4, Mek4, Hek, Tyro4, Hek4), EphA4 (also known as Sek, Sek1, Cek8, Hek8, Tyro1), EphA5 (also known as Ehk1, Bsk, Cek7, Hek7, and Rek7), EphA6 (Ehk2, and Hek12) EphA7 (also known as Mdk1, Hek11, Ehk3, Ebk, Cek11), and EphA8 (also known as Eek, Hek3). The group that includes receptors interacting preferentially with ephrin B proteins is called Eph B and includes EphB1 (also known as Elk, Cek6, Net, Hek6), EphB2 (also known as Cek5, Nuk, Erk, Qek5, Tyro5, Sek3, hek5, Drt), EphB3 (also known as Cek10, Hek2, Mdk5, Tyro6, and Sek4), EphB4 (also known as Htk, Myk1, Tyro11, Mdk2), EphB5 (also known as Cek9, Hek9), and EphB6 (also known as Mep).

"Ephrin" refers to a class of ligands which are anchored to the cell membrane through a transmembrane domain, and bind to the extracellular domain of an Eph receptor, facilitating dimerization and autophosphorylation of the receptor and autophosphorylation of the ligand. The ephrin-A ligands (GPI-anchored ligands) are ephrin-A (also known as B61, LERK1, EFL-1), ephrin-A2 (also known as LERK6, Elf1, mCek7-L, cElf1), ephrin-A3 (also known as LERK3, Ehk1-L, and EFL-2), ephrin-A4 (also known as LERK4, EFL-4, mLERK4), ephrin-A5 (AL1, LERK7, EFL-5, mAL1, [rLERK7], RAGS). The

ephrin-B ligands (transmembrane ligands) are ephrin-B1 (also known as LEKR2, ELK-L, EFL-3, Cek5-L, Stra1, [LERK2]), ephrin-B2 (also known as LERK5, HTK-L, NLERK1, Elf2, Htk-L), and ephrin-B3 (also known as LERK8, ELK-L3, NLERK2, EFL-6, Elf3, [rELK-L3]).

RTKs may be derivable from a variety of sources, including viruses, bacteria, fungi, plants and animals. In a preferred embodiment an RTK is derivable from a mammal, for example, a human.

An RTK in the present invention may be a wild type enzyme, or part thereof, or a mutant, variant or homolog of such an enzyme.

The term "wild type" refers to a polypeptide having a primary amino acid sequence which is identical with the native enzyme (for example, the human enzyme).

The term "mutant" refers to a polypeptide having a primary amino acid sequence which differs from the wild type sequence by one or more amino acid additions, substitutions or deletions. Preferably, the mutant has at least 90% sequence identity with the wild type sequence. Preferably, the mutant has 20 mutations or less over the whole wild-type sequence. More preferably the mutant has 10 mutations or less, most preferably 5 mutations or less over the whole wild-type sequence.

The term "variant" refers to a naturally occurring polypeptide which differs from a wild-type sequence. A variant may be found within the same species (i.e. if there is more than one isoform of the enzyme) or may be found within a different species. Preferably the variant has at least 90% sequence identity with the wild type sequence. Preferably, the variant has 20 mutations or less over the whole wild-type sequence. More preferably, the variant has 10 mutations or less, most preferably 5 mutations or less over the whole wild-type sequence.

The term "part" indicates that the polypeptide comprises a fraction of the wild-type amino acid sequence. It may comprise one or more large contiguous sections of sequence or a plurality of small sections. The "part" may comprise a binding pocket as described herein. The polypeptide may also comprise other elements of sequence, for example, it may be a fusion protein with another protein (such as one which aids isolation or crystallisation of the polypeptide). Preferably the polypeptide comprises at least 50%, more preferably at least 65%, most preferably at least 80% of the wild-type sequence.

The term "homolog" means a polypeptide having a degree of homology with the wild-type amino acid sequence. The term "homology" refers to a degree of complementarity. There may be partial homology or complete homology. In an embodiment of the invention a RTK is substantially homologous to a wild type enzyme. A sequence that is "substantially homologous" refers to a partially complementary sequence that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid. Inhibition of hybridization of a completely complementary sequence to the target sequence may be examined using a hybridization assay (e.g. Southern or northern blot, solution hybridization, etc.) under conditions of reduced stringency. A sequence that is substantially homologous or a hybridization probe will compete for and inhibit the binding of a completely homologous sequence to the target sequence under conditions of reduced stringency. However, conditions of reduced stringency can be such that non-specific binding is permitted, as reduced stringency conditions require that the binding of two sequences to one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested

using a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% homology or identity). The substantially homologous sequence or probe will not hybridize to the second non-complementary target sequence in the absence of non-specific binding.

A sequence of an RTK may have at least 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, or 99% identity. The phrase "percent identity" or "% identity" refers to the percentage of sequence similarity found in a comparison of two or more amino acid sequences. Percent identity can be determined electronically using conventional programs, e.g., by using the MEGALIGN program (LASERGENE software package, DNASTAR). The MEGALIGN program can create alignments between two or more amino acid sequences according to different methods, e.g., the Clustal Method. (Higgins, D. G. and P. M. Sharp (1988) Gene 73:237-244.) Gaps of low or of no homology between the two amino acid sequences are not included in determining percentage similarity.

In the present context, a homologous sequence is taken to include an amino acid sequence which may have at least 75, 85 or 90% identity, preferably at least 95 or 98% identity to the wild-type sequence. The homologs will comprise the same sites (for example, binding pocket) as the subject amino acid sequence.

A sequence may have deletions, insertions or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent enzyme. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues as long as the secondary binding activity of the substance is retained. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine, valine, glycine, alanine, asparagine, glutamine, serine, threonine, phenylalanine, and tyrosine.

The polypeptide may also have a homologous substitution (substitution and replacement are both used herein to mean the interchange of an existing amino acid residue, with an alternative residue) i.e. like-for-like substitution such as basic for basic, acidic for acidic, polar for polar etc. Non-homologous substitution may also occur i.e. from one class of residue to another or alternatively involving the inclusion of unnatural amino acids such as ornithine (hereinafter referred to as Z), diaminobutyric acid ornithine (hereinafter referred to as B), norleucine ornithine (hereinafter referred to as O), pyriylalanine, thienylalanine, naphthylalanine and phenylglycine.

BINDING POCKET

"Binding pocket" refers to a region or site of a RTK or molecular complex thereof that as a result of its shape, associates with another region of the RTK or with a ligand or a part thereof. A binding pocket may regulate the kinase domain of the RTK. A binding pocket may be involved in maintaining an autoinhibited state or active state of an RTK. For example, a binding pocket may comprise part of a juxtamembrane region of an RTK that associates with a kinase domain of the RTK (e.g. strand segment Ex1), a site formed by interacting amino acid residues in the juxtamembrane region (e.g. switch region 2),

a site formed by interacting amino acid residues in the juxtamembrane region and kinase domain (switch region 1), or a region responsible for binding a ligand.

The invention contemplates a binding pocket of an RTK in an autoinhibited state or an active state.

A "ligand" refers to a compound or entity that associates with a binding pocket including nucleotides or analogues or parts thereof, substrates or analogues or parts thereof, or modulators of RTKs, including inhibitors. A ligand may be designed rationally by using a model according to the present invention.

In an aspect of the invention a binding pocket comprises one or more of the residues involved in coordination of a nucleotide or analog thereof, in particular the amino acid residues involved in coordinating the sugar and phosphate groups of the nucleotide.

In an aspect of the invention the binding pocket comprises phosphoregulatory sites of a juxtamembrane region or kinase domain. Phosphoregulatory sites are sites that are autophosphorylated following ligand binding of an RTK and that potentiate binding of cytoplasmic signalling targets such as SH2 or SH3 domain signalling proteins. In a specific aspect the binding pocket comprises invariant tyrosine residues (e.g. tyrosines 596 and 602 of EphA4; tyrosines 604 and 610 of EphB2) within a conserved amino acid sequence (e.g. YIDPFTYEPD in EphB2) in the juxtamembrane region

A binding pocket may comprise one or more of the amino acid residues for an Eph receptor crystal identified as numbers 1 through 49 shown in Table 2. In an aspect the binding pocket comprises the atomic contacts of atomic interactions 1 to 24 (juxtamembrane-kinase interactions) or interactions 25 to 49 (juxtamembrane-juxtamembrane interactions) identified in Table 2. In a preferred embodiment the binding pocket comprises atomic interactions or atomic contacts 27, 28, 29, and 38; 39 and 40; or 9, 13, 14, 16, 18, 19, 32, 39, 40, and 42 in Table 2. In an aspect of the invention the binding pocket comprises all of the amino acid residues identified in Table 2.

A binding pocket may be involved in coordination of a ligand or substrate. For example a binding pocket may be involved in coordination of a nucleotide, or part or analog thereof. Therefore, a binding pocket may comprise two or more of the amino acid residues Phe 709, Met 710 Glu 708, Thr 707, Leu 761, Gly 713, (Lys 661), Ala 659, Ile 691, and (Ser 771) of an RTK structure as described herein, that are capable of associating with or coordinating a nucleotide as described herein.

The term "binding pocket" (BP) also includes a homolog of the binding pocket or a portion thereof. As used herein, the term "homolog" in reference to a binding pocket refers to a binding pocket or a portion thereof which may have deletions, insertions or substitutions of amino acid residues as long as the binding specificity is retained. In this regard, deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues as long as the binding specificity of the binding pocket is retained.

As used herein, the term "portion thereof" means the structural coordinates corresponding to a sufficient number of amino acid residues of a binding pocket (or homologs thereof) that are capable of providing an autoinhibited or active state or for associating with a ligand. For example, the structural

coordinates provided in a crystal structure may contain a subset of the amino acid residues in a binding pocket which may be useful in the modelling and design of compounds that bind to the binding pocket.

AUTOINHIBITED/ACTIVE STATE

An RTK or a binding pocket thereof may be in an autoinhibited state or active state. An "autoinhibited state" refers to the state of a RTK or a binding pocket that results in disruption of the activation segment of the kinase domain and effective coordination of bound nucleotide. The autoinhibited state results in perturbed catalytic function of an RTK. An autoinhibited state typically occurs in the absence of phosphorylation of the RTK.

An "active state" refers to the state of a RTK or a binding pocket that does not result in disruption of the activation segment of the kinase domain and effective coordination of bound nucleotide. In the active state the RTK is catalytically active and the juxtamembrane segment is free to bind to signalling proteins such as SH2 domain containing proteins, including p120-RasGAP, Nck, phosphatidylinositol 3'-kinase, SHEP-1, Src family kinases, and the adapter protein Nck. An active state typically occurs in the presence of phosphorylation of the RTK.

CRYSTAL

The invention provides crystal structures. As used herein, the term "crystal" or "crystalline" means a structure (such as a three dimensional (3D) solid aggregate) in which the plane faces intersect at definite angles and in which there is a regular structure (such as internal structure) of the constituent chemical species. Thus, the term "crystal" can include any one of: a solid physical crystal form such as an experimentally prepared crystal, a crystal structure derivable from the crystal (including secondary and/or tertiary and/or quaternary structural elements), a 2D and/or 3D model based on the crystal structure, a representation thereof such as a schematic representation thereof or a diagrammatic representation thereof, or a data set thereof for a computer.

In one aspect, the crystal is usable in X-ray crystallography techniques. Here, the crystals used can withstand exposure to X-ray beams used to produce a diffraction pattern data necessary to solve the X-ray crystallographic structure. A crystal may be characterized as being capable of diffracting x-rays in a pattern defined by one of the crystal forms depicted in Blundel et al 1976, Protein Crystallography, Academic Press.

A crystal of the invention is generally produced in a laboratory; that is, it is an isolated crystal produced by an individual.

The invention contemplates a crystal comprising a binding pocket of the invention, in particular a binding pocket that regulates the kinase domain of the receptor tyrosine kinase. The binding pocket may be of an autoinhibited state RTK or an active RTK.

In an aspect of the invention a crystal is provided that comprises the juxtamembrane region and kinase domain of an RTK. In an embodiment the RTK is an Eph Receptor, preferably an EphB receptor. In a preferred embodiment the crystal comprises the juxtamembrane region and the catalytic domain (amino acid residues 595 to 906) of EphB2. The juxtamembrane region and the catalytic domain may be in an autoinhibited state.

A crystal of the invention may be characterized by one or more of the following characteristics:

(a) an N-terminal lobe for binding and coordinating ATP for transfer of an α-phosphate to a substrate, comprising a twisted 5-strand β-sheet (denoted β1 to β5) and a single helix αC; and optionally further characterized by (i) a flexible loop that interacts with the adenine base, ribose sugar and the non-hydrolyzable phosphate groups of ATP which loop is formed by β-strands 1 and 2 and a connecting glycine rich segment (g-loop) and (ii) an invariant salt bridge between a lysine side chain in β strand 3 and a glutamic acid side chain in helix αC that coordinates the position of the β-phosphate of ATP; and

(b) a C-terminal lobe comprising two β-strands (β7 and β8) and a series of α-helices (αD to αI) which is further characterized by (i) strands β7 and β8 in the cleft region between the N- and C- terminal lobes where they contribute side chains that participate in catalysis and the binding of magnesium for the coordination of ATP phosphate groups, (ii) an activation segment flanked by the sequence Asp-Phe-Gly of sub-domain VII and Pro-Ile-Arg of sub-domain VIII, and (iii) a helix αI adjacent to helix αH.

A crystal of the invention comprising a juxtamembrane region of an RTK, in particular an Eph receptor, more particularly an EphB receptor, most particularly an EphB2 receptor, may be characterized as comprising a single-turn helix $\alpha A'$ (i.e. a 3/10 helix), and a four-turn helix αB^1 from the amino terminus of an extended strand segment Ex1. The crystal may also comprise this juxtamemembrane region in association with interacting amino acid residues on the N- and C-terminal lobes of the RTK. (See Figures 2-4, and Table 2.)

A crystal of the invention may comprise a juxtamembrane strand segment Ex1 comprising amino acid residues Lys 602 to Ile 605 which strand extends along the cleft region between the N-and C-terminal lobes of an RTK. The strand is stabilized by hydrogen bonding interactions involving the amide group of Phe 604 with the carbonyl group of Met 748 and the Gln 684 side chain with the backbone amide and carbonyl groups of Ile 605.

In a further aspect of the invention a crystal is provided comprising a hydrophobic interface site (referred to herein as switch region 1) comprising side chains of Met 748 and Tyr 750 of the C-terminal kinase lobe; Phe 685 and Ile 681 from helix αC, and Pro 607 from the juxtamembrane helix αA^1, and the phosphoregulatory site or residue Phe 604 which orients into the site.

A crystal of the invention may comprise helix αA^1 which is more particularly characterized by one or more of the following characteristics:

(a) it is composed of a single rigid turn initiated by Asp 606 and Pro 607 and terminated by Thr 609;

(b) it is stabilized by the conformational regidity of Pro 607 and the capping interactions involving Asp 606 and Thr 609 with the free backbone amino group and carbonly groups of Phe 608 and Asp 606.

A crystal of the invention may comprise helix αB^1 which is more particularly characterized by one or more of the following characteristics:

(a) it is initiated by an Asp Pro sequence (residues 612 and 613); and

(b) Asp 612 makes capping interactions with the backbone amino and side chain of Asn 614.

A crystal of the invention may comprise helices αA' and αB' of a juxtamembrane region of an RTK and the portion of the N-terminal lobe of the kinase domain centering on helix αC of the RTK which forms an interface with helices αA' and αB' and is further characterized as follows:

(a) hydrophobic side chains projecting from αA' and αB' include Pro 607, Phe 608, Pro 613, Val 617, Phe620 and Ala 621 which residues associate intimately with the side chains of Arg 673, Leu 676, and Ile 681 from helix αC and the side chains of Leu 693 and Val 696 from β-strand 4;

(b) a hydrogen bond interaction (2.9Å) between Asn 614 and Arg 672; and

(c) the small side chains at positions 616 (Ala), 677 (Ser) and 680 (Ser) facilitate the close packing of helices αA', αB' and αC.

A crystal of the invention may comprise a hydrophobic interface site (also referred to herein as "switch region 2") formed by association of helix αC, strand Ex1 and helices αA' and αB' of the juxtamembrane region of an RTK. The interface is characterized as follows:

(a) projection of the side chain of the phosphoregulatory residue Tyr/Phe 610 onto the surface of the site;

(b) composed of the side chains of Ile 605 from strand Ex1 and the side chains of Ala 616 and Phe 620 from helix αB'; and

(c) an electrostatic environment dominated by Asp 606, Glu 611, Asp 612, Glu 615, and Glu 619.

A crystal of the invention may comprise the following amino acids residues:

(a) Arg 672, Phe Arg 672, Phe 675, and Leu 676 from helix αC, Tyr 667 from the β3 / αC linker and Leu 663, Val 696, Thr 698, Val 703, and Ile 705; or

(b) Met 748, Tyr 750, Phe 685, Ile 681, Pro 607, and Phe 604; or

(c) Phe 709, Met 710, Glu 708, Thr 707, Leu 761, Gly 713, Ala 659, Ile 691, Lys 661, and Ser 771; or

(d) Asp 606, Pro 607, Thr 609, Phe 608 and Asp 606; or

(e) Asp 612, Pro 613, Asp 612, and Asn 614; or

(f) Pro 607, Phe 608, Pro 613, Val 617, Phe 620, Als 621, Arg 673, Leu 676, Ile 681, Leu 693, Val 696, Asn 614, Arg 672, Ala 616, Ser 677, and Ser 680; or

(g) Tyr/Phe 610, Ile 605, Ala 616, Phe 620, Asp 606, Glu 611, Asp 615, and Glu 619.

Preferably the atoms of the amino acid residues in (a) to (g) have the structural coordinates as set out in Table 3.

In an embodiment, a crystal of a Eph receptor of the invention belongs to space group $P2_1$ or P1. The term "space group" refers to the lattice and symmetry of the crystal. In a space group designation the capital letter indicates the lattice type and the other symbols represent symmetry operations that can be carried out on the contents of the asymmetric unit without changing its appearance.

A crystal of the invention may comprise a unit cell having the following unit dimensions: a = 47.05 (± 0.05) Å, b = 57.62 (±0.05) Å, c = 67.74 (±0.05) Å, or a = 47.86 (± 0.05) Å, b = 98.09 (±0.05) Å, c = 68.18 (±0.05) Å. The term "unit cell" refers to the smallest and simplest volume element (i.e. parallelpiped-shaped block) of a crystal that is completely representative of the unit of pattern of the crystal. The unit cell axial lengths are represented by a, b, and c. Those of skill in the art understand that a set of atomic coordinates determined by X-ray crystallography is not without standard error.

In a preferred embodiment, a crystal of the invention has the structural coordinates as shown in Table 3. As used herein, the term "structural coordinates" refers to a set of values that define the position of one or more amino acid residues with reference to a system of axes. The term refers to a data set that defines the three dimensional structure of a molecule or molecules (e.g. Cartesian coordinates, temperature factors, and occupancies). Structural coordinates can be slightly modified and still render nearly identical three dimensional structures. A measure of a unique set of structural coordinates is the root-mean-square deviation of the resulting structure. Structural coordinates that render three dimensional structures (in particular a three dimensional structure of a ligand binding pocket) that deviate from one another by a root-mean-square deviation of less than 5 Å, 4 Å, 3 Å, 2 Å, 1.5 Å. 1.0 Å, or 0.5 Å may be viewed by a person of ordinary skill in the art as very similar.

Variations in structural coordinates may be generated because of mathematical manipulations of the structural coordinates of a glycosyltransferase described herein. For example, the structural coordinates of Table 3 may be manipulated by crystallographic permutations of the structural coordinates, fractionalization of the structural coordinates, integer additions or substractions to sets of the structural coordinates, inversion of the structural coordinates or any combination of the above.

Variations in the crystal structure due to mutations, additions, substitutions, and/or deletions of the amino acids, or other changes in any of the components that make up the crystal may also account for modifications in structural coordinates. If such modifications are within an acceptable standard error as compared to the original structural coordinates, the resulting structure may be the same. Therefore, a ligand that bound to a binding pocket of an RTK, in particular an Eph receptor, would also be expected to bind to another binding pocket whose structural coordinates defined a shape that fell within the acceptable error. Such modified structures of a binding pocket thereof are also within the scope of the invention.

Various computational analyses may be used to determine whether a molecule or the binding pocket thereof is sufficiently similar to all or parts of an RTK or a binding pocket thereof. Such analyses may be carried out using conventional software applications and methods as described herein.

A crystal of the invention may also be specifically characterised by the parameters, diffraction statistics and/or refinement statistics set out in Tables 1.

With reference to a crystal of the present invention, residues in a binding pocket may be defined by their spatial proximity to a ligand in the crystal structure. For example, a binding pocket may be defined by its proximity to a nucleotide, substrate molecule, or modulator.

A crystal of the invention may comprise a binding pocket that is involved in coordination of a nucleotide, or part or analog thereof. Therefore, a crystal may comprise a binding pocket comprising two

or more of the amino acid residues Phe 709, Met 710 Glu 708, Thr 707, Leu 761, Gly 713, (Lys 661), Ala 659, Ile 691, and (Ser 771) of an RTK structure as described herein, that are capable of associating with or coordinating a nucleotide as described herein.

A crystal or secondary or three-dimensional structure of a binding pocket of an RTK, in particular an EphB2 receptor, may be specifically defined by one or more of the atomic contacts of the atomic interactions identified in Table 2. The atomic interactions in Table 2 are defined therein by an atomic contact (more preferably, a specific atom of an amino acid residue where indicated) on the juxtamembrane region, and an atomic contact (more preferably, a specific atom of an amino acid residue where indicated) on the kinase domain, juxtamembrane region, or ligand. In certain embodiments, a crystal of the invention comprises the atomic contacts of atomic interactions 1 to 24 (juxtamembrane-kinase interactions) or atomic interactions 25 to 49 (juxtamembrane-juxtamembrane interactions) identified in Table 2. In certain particular embodiments a crystal is provided comprising the atomic contacts of atomic interactions 27, 28, 29, and 38; 39 and 40; or 9, 13, 14, 16, 18, 19, 32, 39, 40, and 42.

Preferably, a crystal is defined by the atoms of the atomic contacts in the binding pocket having the structural coordinates for the atoms listed in Table 3.

A crystal of the invention includes a binding pocket in association with one or more moieties, including heavy-metal atoms i.e. a derivative crystal, or one or more ligands or molecules i.e. a co-crystal.

The term "associate", "association" or "associating" refers to a condition of proximity between a moiety (i.e. chemical entity or compound or portions or fragments thereof), and a binding pocket. The association may be non-covalent i.e. where the juxtaposition is energetically favored by for example, hydrogen-bonding, van der Waals, or electrostatic or hydrophobic interactions, or it may be covalent.

The term "heavy-metal atoms" refers to an atom that can be used to solve an x-ray crystallography phase problem, including but not limited to a transition element, a lanthanide metal, or an actinide metal. Lanthanide metals include elements with atomic numbers between 57 and 71, inclusive. Actinide metals include elements with atomic numbers between 89 and 103, inclusive.

Multiwavelength anomalous diffraction (MAD) phasing may be used to solve protein structures using selenomethionyl (SeMet) proteins. Therefore, a complex of the invention may comprise a crystalline binding pocket with selenium on the methionine residues of the protein.

A crystal may comprise a complex between a binding pocket and one or more ligands or molecules. In other words the binding pocket may be associated with one or more ligands or molecules in the crystal. The ligand may be any compound that is capable of stably and specifically associating with the binding pocket. A ligand may, for example, be a modulator of an Eph receptor, or a nucleotide or substrate or analogue thereof.

In an embodiment of the invention, a binding pocket is in association with a cofactor in the crystal. A "cofactor" refers to a molecule required for RTK enzyme activity and/or stability. For example, the cofactor may be a metal ion, including magnesium and other similar atoms or metals.

In an embodiment, a crystal of the invention comprises a complex between a binding pocket, and a nucleotide or analogue thereof and/or a substrate or analogue thereof. A "nucleotide" includes ATP,

ADP, AMP, or analogues thereof, for example, β,γ-imidoadenosine-5'-triphosphate (AMP-PNP, STI-571, and quercetin. A substrate may be for example, a signalling protein, or another portion of the same RTK (e.g juxtamembrane-kinase domain complex). An analog of a nucleotide or substrate is one which mimics the nucleotide or substrate molecule, binding in the binding pocket, but which is incapable (or has a significantly reduced capacity) to take part in a kinase reaction.

Therefore, the present invention also provides:

(a) a crystal comprising a binding pocket of an RTK and a nucleotide or analogue thereof;

(b) a crystal comprising a binding pocket of an RTK and a substrate or analogue thereof;

(c) a crystal comprising a binding pocket of an RTK and a nucleotide or analogue thereof, and a substrate or analogue thereof.

A complex may comprise one or more of the intermolecular interactions identified in Table 2. A structure of a complex of the invention may be defined by selected intermolecular contacts, preferably the structural coordinates of the intermolecular contacts as defined in Table 3.

A crystal of the invention may enable the determination of structural data for a ligand. In order to be able to derive structural data for a ligand, it is necessary for the molecule to have sufficiently strong electron density to enable a model of the molecule to be built using standard techniques. For example, there should be sufficient electron density to allow a model to be built using XTALVIEW (McRee 1992 J. Mol. Graphics. 10 44-46).

Illustrations of particular crystals of the invention are shown in Figures 2, 3, and 4.

METHOD OF MAKING A CRYSTAL

The present invention also provides a method of making a crystal according to the invention. The crystal may be formed from an aqueous solution comprising a purified polypeptide comprising an RTK, in particular an Eph receptor including a variant, part, homolog, or fragment thereof (e.g. a binding pocket). A method may utilize a purified polypeptide comprising a binding pocket to form a crystal. A method may utilize a purified polypeptide comprising a juxtamembrane region and kinase domain of an RTK, in particular an Eph receptor, preferably an EphB receptor, or more preferably an EphB2 receptor.

The term "purified" in reference to a polypeptide, does not require absolute purity such as a homogenous preparation rather it represents an indication that the polypeptide is relatively purer than in the natural environment. Generally, a purified polypeptide is substantially free of other proteins, lipids, carbohydrates, or other materials with which it is naturally associated, preferably at a functionally significant level for example at least 85% pure, more preferably at least 95% pure, most preferably at least 99% pure. A skilled artisan can purify a polypeptide comprising using standard techniques for protein purification. A substantially pure polypeptide will yield a single major band on a non-reducing polyacrylamide gel. Purity of the polypeptide can also be determined by amino-terminal amino acid sequence analysis.

A polypeptide used in the method may be chemically synthesized in whole or in part using techniques that are well-known in the art. Alternatively, methods are well known to the skilled artisan to construct expression vectors containing a native or mutated RTK coding sequence and appropriate

transcriptional/translational control signals. These methods include *in vitro* recombinant DNA techniques, synthetic techniques, and *in vivo* recombination/genetic recombination. See for example the techniques described in Sambrook et al. (Molecular Cloning: A Laboratory Manual, 2nd Edition, Cold Spring Harbor Laboratory press (1989)), and other laboratory textbooks. (See also Sarker et al, Glycoconjugate J. 7:380, 1990; Sarker et al, Proc. Natl. Acad, Sci. USA 88:234-238, 1991, Sarker et al, Glycoconjugate J. 11: 204-209, 1994; Hull et al, Biochem Biophys Res Commun 176:608, 1991 and Pownall et al, Genomics 12:699-704, 1992).

Crystals may be grown from an aqueous solution containing the purified polypeptide by a variety of conventional processes. These processes include batch, liquid, bridge, dialysis, vapor diffusion, and hanging drop methods. (See for example, McPherson, 1982 John Wiley, New York; McPherson, 1990, Eur. J. Biochem. 189: 1-23; Webber. 1991, Adv. Protein Chem. 41:1-36). Generally, native crystals of the invention are grown by adding precipitants to the concentrated solution of the polypeptide. The precipitants are added at a concentration just below that necessary to precipitate the protein. Water is removed by controlled evaporation to produce precipitating conditions, which are maintained until crystal growth ceases.

Derivative crystals of the invention can be obtained by soaking native crystals in a solution containing salts of heavy metal atoms. A complex of the invention can be obtained by soaking a native crystal in a solution containing a compound that binds the polypeptide, or they can be obtained by co-crystallizing the polypeptide in the presence of one or more compounds. In order to obtain co-crystals with a compound which binds deep within the tertiary structure of the polypeptide it is necessary to use the second method.

In a preferred embodiment, the polypeptide is co-crystallised with a compound which stabilises the polypeptide (e.g. AMP-PNP).

Once the crystal is grown it can be placed in a glass capillary tube and mounted onto a holding device connected to an X-ray generator and an X-ray detection device. Collection of X-ray diffraction patterns are well documented by those skilled in the art (See for example, Ducruix and Geige, 1992, IRL Press, Oxford, England). A beam of X-rays enter the crystal and diffract from the crystal. An X-ray detection device can be utilized to record the diffraction patterns emanating from the crystal. Suitable devices include the Marr 345 imaging plate detector system with an RU200 rotating anode generator.

Multiwavelength anomalous diffraction (MAD) phasing using selenomethionyl (SeMet) proteins may be used to determine a crystal of the invention. Thus, the invention contemplates a method for determining a crystal structure of the invention using a selenomethionyl derivative of an RTK, including a variant, part, homolog or fragement thereof.

Methods for obtaining the three dimensional structure of the crystalline form of a molecule or complex are described herein and known to those skilled in the art (see Ducruix and Geige 1992, IRL Press, Oxford, England). Generally, the x-ray crystal structure is given by the diffraction patterns. Each diffraction pattern reflection is characterized as a vector and the data collected at this stage determines the amplitude of each vector. The phases of the vectors may be determined by the isomorphous replacement

method where heavy atoms soaked into the crystal are used as reference points in the X-ray analysis (see for example, Otwinowski, 1991, Daresbury, United Kingdom, 80-86). The phases of the vectors may also be determined by molecular replacement (see for example, Naraza, 1994, Proteins 11:281-296). The amplitudes and phases of vectors from the crystalline form determined in accordance with these methods can be used to analyze other related crystalline polypeptides.

The unit cell dimensions and symmetry, and vector amplitude and phase information can be used in a Fourier transform function to calculate the electron density in the unit cell i.e. to generate an experimental electron density map. This may be accomplished using the PHASES package (Furey, 1990). Amino acid sequence structures are fit to the experimental electron density map (i.e. model building) using computer programs (e.g. Jones, TA. et al, Acta Crystallogr A47, 100-119, 1991). This structure can also be used to calculate a theoretical electron density map. The theoretical and experimental electron density maps can be compared and the agreement between the maps can be described by a parameter referred to as R-factor. A high degree of overlap in the maps is represented by a low value R-factor. The R-factor can be minimized by using computer programs that refine the structure to achieve agreement between the theoretical and observed electron density map. For example, the XPLOR program, developed by Brunger (1992, Nature 355:472-475) can be used for model refinement.

A three dimensional structure of the molecule or complex may be described by atoms that fit the theoretical electron density characterized by a minimum R value. Files can be created for the structure that defines each atom by coordinates in three dimensions.

MODEL

A crystal structure of the present invention may be used to make a model of a binding pocket of an RTK, preferably an Eph receptor, more preferably an EphB receptor. A model may, for example, be a structural model or a computer model. A model may represent the secondary, tertiary and/or quaternary structure of the binding pocket. The model itself may be in two or three dimensions. It is possible for a computer model to be in three dimensions despite the constraints imposed by a conventional computer screen, if it is possible to scroll along at least a pair of axes, causing "rotation" of the image.

As used herein, the term "modelling" includes the quantitative and qualitative analysis of molecular structure and/or function based on atomic structural information and interaction models. The term "modelling" includes conventional numeric-based molecular dynamic and energy minimization models, interactive computer graphic models, modified molecular mechanics models, distance geometry and other structure-based constraint models.

Preferably, modelling is performed using a computer and may be further optimized using known methods. This is called modelling optimisation.

An integral step to an approach of the invention for designing modulators (e.g. inhibitors) of a subject receptor involves construction of computer graphics models of the binding pocket of a receptor which can be used to design pharmacophores by rational drug design. For instance, for an inhibitor to interact optimally with the subject binding pocket, it will generally be desirable that it have a shape which is at least partly complimentary to that of a particular binding pocket of the receptor, as for example those

binding pockets of the receptor which are involved in recognition of a ligand, regulating the kinase domain, or regulating signal transduction. Additionally, other factors, including electrostatic interactions, hydrogen bonding, hydrophobic interactions, desolvation effects, and cooperative motions of ligand and receptor, all influence the binding effect and should be taken into account in attempts to design bioactive modulators (e.g. inhibitors).

As described herein, a computer-generated molecular model of the subject receptors can be created. In preferred embodiments, at least the Cα-carbon positions of the RTK sequence of interest are mapped to a particular coordinate pattern, such as the coordinates for a binding pocket of an EphB2 shown in Table 3, by homology modeling, and the structure of the protein and velocities of each atom are calculated at a simulation temperature (T_o) at which the docking simulation is to be determined. Typically, such a protocol involves primarily the prediction of side-chain conformations in the modeled protein, while assuming a main-chain trace taken from a tertiary structure such as provided in Table 3 and the Figures. Computer programs for performing energy minimization routines are commonly used to generate molecular models. For example, both the CHARMM (Brooks et al. (1983) *J Comput Chem* 4:187-217) and AMBER (Weiner et al (1981) *J. Comput. Chem.* 106: 765) algorithms handle all of the molecular system setup, force field calculation, and analysis (see also, Eisenfield et al. (1991) *Am J Physiol* 261:C376-386; Lybrand (1991) *J Pharm Belg* 46:49-54; Froimowitz (1990) *Biotechniques* 8:640-644; Burbam et al. (1990) *Proteins* 7:99-111; Pedersen (1985) *Environ Health Perspect* 61:185-190; and Kini et al. (1991) *J Biomol Struct Dyn* 9:475-488). At the heart of these programs is a set of subroutines that, given the position of every atom in the model, calculate the total potential energy of the system and the force on each atom. These programs may utilize a starting set of atomic coordinates, such as the coordinates provided in Table 3, the parameters for the various terms of the potential energy function, and a description of the molecular topology (the covalent structure). Common features of such molecular modeling methods include: provisions for handling hydrogen bonds and other constraint forces; the use of periodic boundary conditions; and provisions for occasionally adjusting positions, velocities, or other parameters in order to maintain or change temperature, pressure, volume, forces of constraint, or other externally controlled conditions.

Most conventional energy minimization methods use the input data described above and the fact that the potential energy function is an explicit, differentiable function of Cartesian coordinates, to calculate the potential energy and its gradient (which gives the force on each atom) for any set of atomic positions. This information can be used to generate a new set of coordinates in an effort to reduce the total potential energy and, by repeating this process over and over, to optimize the molecular structure under a given set of external conditions. These energy minimization methods are routinely applied to molecules similar to the subject RTK proteins as well as nucleic acids, polymers and zeolites.

In general, energy minimization methods can be carried out for a given temperature, T_i, which may be different than the docking simulation temperature, T_o. Upon energy minimization of the molecule at T_i, coordinates and velocities of all the atoms in the system are computed. Additionally, the normal modes of the system are calculated. It will be appreciated by those skilled in the art that each normal mode

is a collective, periodic motion, with all parts of the system moving in phase with each other, and that the motion of the molecule is the superposition of all normal modes. For a given temperature, the mean square amplitude of motion in a particular mode is inversely proportional to the effective force constant for that mode, so that the motion of the molecule will often be dominated by the low frequency vibrations.

After the molecular model has been energy minimized at T_i, the system is "heated" or "cooled" to the simulation temperature, T_o, by carrying out an equilibration run where the velocities of the atoms are scaled in a step-wise manner until the desired temperature, T_o, is reached. The system is further equilibrated for a specified period of time until certain properties of the system, such as average kinetic energy, remain constant. The coordinates and velocities of each atom are then obtained from the equilibrated system.

Further energy minimization routines can also be carried out. For example, a second class of methods involves calculating approximate solutions to the constrained EOM for the protein. These methods use an iterative approach to solve for the Lagrange multipliers and, typically, only need a few iterations if the corrections required are small. The most popular method of this type, SHAKE (Ryckaert et al. (1977) *J Comput Phys* 23:327; and Van Gunsteren et al. (1977) *Mol Phys* 34:1311) is easy to implement and scales as O(N) as the number of constraints increases. Therefore, the method is applicable to macromolecules such as the RTK proteins of the present invention. An alternative method, RATTLE (Anderson (1983) *J Comput Phys* 52:24) is based on the velocity version of the Verlet algorithm. Like SHAKE, RATTLE is an iterative algorithm and can be used to energy minimize the model of the subject protein.

Overlays and super positioning with a three dimensional model of a binding pocket of the invention may be used for modelling optimisation. Additionally alignment and/or modelling can be used as a guide for the placement of mutations on a binding pocket to characterize the nature of the site in the context of a cell.

The three dimensional structure of a new crystal may be modelled using molecular replacement. The term "molecular replacement" refers to a method that involves generating a preliminary model of a molecule or complex whose structural coordinates are unknown, by orienting and positioning a molecule whose structural coordinates are known within the unit cell of the unknown crystal, so as best to account for the observed diffraction pattern of the unknown crystal. Phases can then be calculated from this model and combined with the observed amplitudes to give an approximate Fourier synthesis of the structure whose coordinates are unknown. This, in turn, can be subject to any of the several forms of refinement to provide a final, accurate structure of the unknown crystal. Lattman, E., "Use of the Rotation and Translation Functions", in Methods in Enzymology, 115, pp. 55-77 (1985); M. G. Rossmann, ed., "The Molecular Replacement Method", Int. Sci. Rev. Ser., No. 13, Gordon & Breach, New York, (1972).

Commonly used computer software packages for molecular replacement are X-PLOR (Brunger 1992, Nature 355: 472-475), AMoRE (Navaza, 1994, Acta Crystallogr. A50:157-163), the CCP4 package (Collaborative Computational Project, Number 4, "The CCP4 Suite: Programs for Protein Crystallography", Acta Cryst., Vol. D50, pp. 760-763, 1994), the MERLOT package (P.M.D. Fitzgerald,

J. Appl. Cryst., Vol. 21, pp. 273-278, 1988) and XTALVIEW (McCree et al (1992) J. Mol. Graphics 10: 44-46. It is preferable that the resulting structure not exhibit a root-mean-square deviation of more than 3 Å.

Molecular replacement computer programs generally involve the following steps: (1) determining the number of molecules in the unit cell and defining the angles between them (self rotation function); (2) rotating the known structure against diffraction data to define the orientation of the molecules in the unit cell (rotation function); (3) translating the known structure in three dimensions to correctly position the molecules in the unit cell (translation function); (4) determining the phases of the X-ray diffraction data and calculating an R-factor calculated from the reference data set and from the new data wherein an R-factor between 30-50% indicates that the orientations of the atoms in the unit cell have been reasonably determined by the method; and (5) optionally, decreasing the R-factor to about 20% by refining the new electron density map using iterative refinement techniques known to those skilled in the art (refinement).

The quality of the model may be analysed using a program such as PROCHECK or 3D-Profiler [Laskowski et al 1993 J. Appl. Cryst. 26:283-291; Luthy R. et al, Nature 356: 83-85, 1992; and Bowie, J.U. et al, Science 253: 164-170, 1991]. Once any irregularities have been resolved, the entire structure may be further refined.

Other molecular modelling techniques may also be employed in accordance with this invention. See, e.g., Cohen, N. C. *et al*, "Molecular Modelling Software and Methods for Medicinal Chemistry", J. Med. Chem., 33, pp. 883-894 (1990). See also, Navia, M. A. and M. A. Murcko, "The Use of Structural Information in Drug Design", Current Opinions in Structural Biology, 2, pp. 202-210 (1992).

Using the structural coordinates of crystal provided by the invention, molecular modelling may be used to determine the structural coordinates of a crystalline mutant or homolog of an RTK binding pocket. By the same token a crystal of the invention can be used to provide a model of a ligand. Modelling techniques can then be used to approximate the three dimensional structure of ligand derivatives and other components which may be able to mimic the atomic contacts between a ligand and binding pocket.

COMPUTER FORMAT OF CRYSTALS/MODELS

Information derivable from a crystal of the present invention (for example the structural coordinates) and/or the model of the present invention may be provided in a computer-readable format.

Therefore, the invention provides a computer readable medium or a machine readable storage medium which comprises the structural coordinates of a binding pocket of an RTK including all or any parts thereof, or ligands including portions thereof. Such storage medium or storage medium encoded with these data are capable of displaying on a computer screen or similar viewing device, a three-dimensional graphical representation of a molecule or molecular complex which comprises such binding pockets or similarly shaped homologous binding pockets. Thus, the invention also provides computerized representations of the secondary or three-dimensional structures of a binding pocket of the invention, including any electronic, magnetic, or electromagnetic storage forms of the data needed to define the structures such that the data will be computer readable for purposes of display and/or manipulation.

In an aspect the invention provides a computer for producing a three-dimensional representation of a molecule or molecular complex, wherein said molecule or molecular complex comprises a binding pocket defined by structural coordinates of a binding pocket or structural coordinates of atoms of a ligand, or a three-dimensional representation of a homolog of said molecule or molecular complex, wherein said homolog comprises a binding pocket or ligand that has a root mean square deviation from the backbone atoms not more than 1.5 angstroms wherein said computer comprises:

(a) a machine-readable data storage medium comprising a data storage material encoded with machine readable data wherein said data comprises the structural coordinates of a binding pocket of an RTK or a ligand according to Table 3;

(b) a working memory for storing instructions for processing said machine-readable data;

(c) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and

(d) a display coupled to said central-processing unit for displaying said three-dimensional representation.

The invention also provides a computer for determining at least a portion of the structural coordinates corresponding to an X-ray diffraction pattern of a molecule or molecular complex wherein said computer comprises:

(a) a machine-readable data storage medium comprising a data storage material encoded with machine readable data wherein said data comprises the structural coordinates according to Table 3;

(b) a machine-readable data storage medium comprising a data storage material encoded with machine readable data wherein said data comprises an X-ray diffraction pattern of said molecule or molecular complex;

(c) a working memory for storing instructions for processing said machine-readable data of (a) and (b);

(d) a central-processing unit coupled to said working memory and to said machine-readable data storage medium of (a) and (b) for performing a Fourier transform of the machine readable data of (a) and for processing said machine readable data of (b) into structural coordinates; and

(e) a display coupled to said central-processing unit for displaying said structural coordinates of said molecule or molecular complex.

STRUCTURAL STUDIES

The present invention also provides a method for determining the secondary and/or tertiary structures of a polypeptide or part thereof by using a crystal, or a model according to the present invention. The polypeptide or part thereof may be any polypeptide or part thereof for which the secondary and or tertiary structure is uncharacterised or incompletely characterised. In a preferred embodiment the polypeptide shares (or is predicted to share) some structural or functional homology to a crystal of the

present invention. For example, the polypeptide may show a degree of structural homology over some or all parts of the primary amino acid sequence.

The polypeptide may be an RTK, preferably an Eph receptor with a different specificity for a nucleotide, or substrate. The polypeptide may be an RTK preferably an Eph receptor which requires a different metal cofactor. Alternatively (or in addition) the polypeptide may be an RTK, preferably an Eph receptor from a different species.

The polypeptide may be a mutant of a wild-type RTK, in particular an Eph receptor. A mutant may arise naturally, or may be made artificially (for example using molecular biology techniques). The mutant may also not be "made" at all in the conventional sense, but merely tested theoretically using the model of the present invention. A mutant may or may not be functional.

Thus, using a model of the present invention, the effect of a particular mutation on the overall two and/or three dimensional structure of an RTK, in particular an Eph receptor, the autoinhibited state or active state, and/or the interaction between a binding pocket of the enzyme and a ligand can be investigated.

Alternatively, the polypeptide may perform an analogous function or be suspected to show a similar catalytic mechanism to an RTK, in particular an Eph receptor.

The polypeptide may also be the same as the polypeptide of the crystal, but in association with a different ligand (for example, modulator or inhibitor) or cofactor. In this way it is possible to investigate the effect of altering the ligand or compound with which the polypeptide is associated on the structure of the binding pocket.

Secondary or tertiary structure may be determined by applying the structural coordinates of the crystal or model of the present invention to other data such as an amino acid sequence, X-ray crystallographic diffraction data, or nuclear magnetic resonance (NMR) data. Homology modeling, molecular replacement, and nuclear magnetic resonance methods using these other data sets are described below.

Homology modeling (also known as comparative modeling or knowledge-based modeling) methods develop a three dimensional model from a polypeptide sequence based on the structures of known proteins (i.e. an RTK, in particular an Eph receptor, of the crystal). The method utilizes a computer model of a crystal of the present invention (the "known structure"), a computer representation of the amino acid sequence of the polypeptide with an unknown structure, and standard computer representations of the structures of amino acids. The method in particular comprises the steps of; (a) identifying structurally conserved and variable regions in the known structure; (b) aligning the amino acid sequences of the known structure and unknown structure (c) generating co-ordinates of main chain atoms and side chain atoms in structurally conserved and variable regions of the unknown structure based on the coordinates of the known structure thereby obtaining a homology model; and (d) refining the homology model to obtain a three dimensional structure for the unknown structure. This method is well known to those skilled in the art (Greer, 1985, Science 228, 1055; Bundell et al 1988, Eur. J. Biochem. 172, 513; Knighton et al., 1992, Science 258:130-135, http://biochem.vt.edu/courses/modeling/ homology.htn). Computer programs that

can be used in homology modelling are Quanta and the Homology module in the Insight II modelling package distributed by Molecular Simulations Inc, or MODELLER (Rockefeller University, www.iucr.ac.uk/sinris-top/logical/prg-modeller.html).

In step (a) of the homology modelling method, a known structure is examined to identify the structurally conserved regions (SCRs) from which an average structure, or framework, can be constructed for these regions of the protein. Variable regions (VRs), in which known structures may differ in conformation, also must be identified. SCRs generally correspond to the elements of secondary structure, such as alpha-helices and beta-sheets, and to ligand- and substrate-binding sites (e.g. nucleotide binding sites). The VRs usually lie on the surface of the proteins and form the loops where the main chain turns.

Many methods are available for sequence alignment of known structures and unknown structures. Sequence alignments generally are based on the dynamic programming algorithm of Needleman and Wunsch [J. Mol. Biol. 48: 442-453, 1970]. Current methods include FASTA, Smith-Waterman, and BLASTP, with the BLASTP method differing from the other two in not allowing gaps. Scoring of alignments typically involves construction of a 20x20 matrix in which identical amino acids and those of similar character (i.e., conservative substitutions) may be scored higher than those of different character. Substitution schemes which may be used to score alignments include the scoring matrices PAM (Dayhoff et al., Meth. Enzymol. 91: 524-545, 1983), and BLOSUM (Henikoff and Henikoff, Proc. Nat. Acad. Sci. USA 89: 10915-`0919, 1992), and the matrices based on alignments derived from three-dimensional structures including that of Johnson and Overington (JO matrices) (J. Mol. Biol. 233: 716-738, 1993).

Alignment based solely on sequence may be used; however, other structural features also may be taken into account. In Quanta, multiple sequence alignment algorithms are available that may be used when aligning a sequence of the unknown with the known structures. Four scoring systems (i.e. sequence homology, secondary structure homology, residue accessibility homology, CA-CA distance homology) are available, each of which may be evaluated during an alignment so that relative statistical weights may be assigned.

When generating coordinates for the unknown structure, main chain atoms and side chain atoms, both in SCRs and VRs need to be modelled. A variety of approaches known to those skilled in the art may be used to assign co-ordinates to the unknown. In particular, the co-ordinates of the main chain atoms of SCRs will be transferred to the unknown structure. VRs correspond most often to the loops on the surface of the polypeptide and if a loop in the known structure is a good model for the unknown, then the main chain co-ordinates of the known structure may be copied. Side chain coordinates of SCRs and VRs are copied if the residue type in the unknown is identical to or very similar to that in the known structure. For other side chain coordinates, a side chain rotamer library may be used to define the side chain coordinates. When a good model for a loop cannot be found fragment databases may be searched for loops in other proteins that may provide a suitable model for the unknown. If desired, the loop may then be subjected to conformational searching to identify low energy conformers if desired.

Once a homology model has been generated it is analyzed to determine its correctness. A computer program available to assist in this analysis is the Protein Health module in Quanta which

provides a variety of tests. Other programs that provide structure analysis along with output include PROCHECK and 3D-Profiler [Luthy R. et al, Nature 356: 83-85, 1992; and Bowie, J.U. et al, Science 253: 164-170, 1991]. Once any irregularities have been resolved, the entire structure may be further refined. Refinement may consist of energy minimization with restraints, especially for the SCRs. Restraints may be gradually removed for subsequent minimizations. Molecular dynamics may also be applied in conjunction with energy minimization.

Molecular replacement involves applying a known structure to solve the X-ray crystallographic data set of a polypeptide of unknown structure. The method can be used to define the phases describing the X-ray diffraction data of a polypeptide of unknown structure when only the amplitudes are known. Thus in an embodiment of the invention, a method is provided for determining three dimensional structures of polypeptides with unknown structure by applying the structural coordinates of a crystal of the present invention to provide an X-ray crystallographic data set for a polypeptide of unknown structure, and (b) determining a low energy conformation of the resulting structure.

The structural coordinates of a crystal of the present invention may be applied to nuclear magnetic resonance (NMR) data to determine the three dimensional structures of polypeptides with uncharacterised or incompletely characterised sturcture. (See for example, Wuthrich, 1986, John Wiley and Sons, New York: 176-199; Pflugrath et al., 1986, J. Molecular Biology 189: 383-386; Kline et al., 1986 J. Molecular Biology 189:377-382). While the secondary structure of a polypeptide may often be determined by NMR data, the spatial connections between individual pieces of secondary structure are not as readily determined. The structural coordinates of a polypeptide defined by X-ray crystallography can guide the NMR spectroscopist to an understanding of the spatial interactions between secondary structural elements in a polypeptide of related structure. Information on spatial interactions between secondary structural elements can greatly simplify Nuclear Overhauser Effect (NOE) data from two-dimensional NMR experiments. In addition, applying the structural coordinates after the determination of secondary structure by NMR techniques simplifies the assignment of NOE's relating to particular amino acids in the polypeptide sequence and does not greatly bias the NMR analysis of polypeptide structure.

In an embodiment, the invention relates to a method of determining three dimensional structures of polypeptides with unknown structures, by applying the structural coordinates of a crystal of the present invention to nuclear magnetic resonance (NMR) data of the unknown structure. This method comprises the steps of: (a) determining the secondary structure of an unknown structure using NMR data; and (b) simplifying the assignment of through-space interactions of amino acids. The term " through-space interactions" defines the orientation of the secondary structural elements in the three dimensional structure and the distances between amino acids from different portions of the amino acid sequence. The term "assignment" defines a method of analyzing NMR data and identifying which amino acids give rise to signals in the NMR spectrum.

SCREENING METHODS

Another aspect of the present invention is the design and identification of agents that inhibit or potentiate an autoinhibition state or active state of an RTK. The rationale design and identification of agents can be accomplished by utilizing the structural coordinates that define a binding pocket of an RTK.

The structures described herein, and the structures of other polypeptides determined by homology modeling, molecular replacement, and NMR techniques described herein can also be applied to modulator design and identification methods.

The invention contemplates molecular models, in particular three-dimensional molecular models of RTK proteins, and their use as templates for the design of agents able to mimic or inhibit ligand activation or autophosphorylation or phoshorylation of the proteins (e.g. modulators). A modulator may inhibit or potentiate an autoinhibited state or alternatively an active state.

In certain embodiments, the present invention provides a method of screening for a ligand that associates with a binding pocket and/or modulates the function of an Eph receptor by using a crystal or a model according to the present invention. The method may involve investigating whether a test compound is capable of associating with or binding a binding pocket, and/or inhibiting or enhancing interactions of atomic contacts in a binding pocket.

In accordance with an aspect of the present invention, a method is provided for screening for a ligand capable of binding to a binding pocket, wherein the method comprises using a crystal or model according to the invention.

In another aspect, the invention relates to a method of screening for a ligand capable of binding to a binding pocket, wherein the binding pocket is defined by the structural coordinates given herein, the method comprising contacting the binding pocket with a test compound and determining if the test compound binds to the binding pocket. The binding pocket may be a binding pocket of an autoinhibited state or an active state. In the case of an autoinhibited state binding pocket the screening method may potentially identify an inhibitor that may disrupt catalytic activity of an RTK, for example,` by maintaining the RTK in an autoinhibited state. A disruption of catalytic activity may be useful in the treatment of conditions involving increased RTK activity e.g. cancer.

In one embodiment, the present invention provides a method of screening for a test compound capable of interacting with one or more key amino acid residues of a binding pocket of an RTK. For example, a test compound that interacts with one or more of Tyr/Phe604 , Tyr/Phe 610, Tyr 667, Tyr 744, and Tyr 750 of EphB2 receptor may prevent phosphorylation of one or more of the tyrosines and thereby promote the autoinhibited state of the receptor.

Another aspect of the invention provides a process comprising the steps of:

(a) performing a method of screening for a ligand described above;

(b) identifying one or more ligands capable of binding to a binding pocket; and

(c) preparing a quantity of said one or more ligands.

A further aspect of the invention provides a process comprising the steps of;

(a) performing a method of screening for a ligand as described above;

(b) identifying one or more ligands capable of binding to a binding pocket; and

(c) preparing a pharmaceutical composition comprising said one or more ligands.

Once a test compound capable of interacting with one or more key amino acid residues in a binding pocket of an RTK has been identified, further steps may be carried out either to select and/or modify compounds and/or to modify existing compounds, to modulate the interaction with the key amino acid residues in the binding pocket.

Yet another aspect of the invention provides a process comprising the steps of;

(a) performing the method of screening for a ligand as described above;

(b) identifying one or more ligands capable of binding to a binding pocket;

(c) modifying said one or more ligands capable of binding to a binding pocket;

(d) performing said method of screening for a ligand as described above; and

(e) optionally preparing a pharmaceutical composition comprising said one or more ligands.

In another aspect of the invention, a method of screening for a test compound is provided comprising screening for test compounds that affect (inhibit or potentiate) a juxtamembrane-juxtamembrane interaction (e.g. interactions 25 to 49 in Table 2) or juxtamembrane-kinase interactions (e.g. interactions 1 to 24 in Table 2) described herein.

As used herein, the term "test compound" means any compound which is potentially capable of associating with a binding pocket, inhibiting or enhancing interactions of atomic contacts in a binding pocket, and/or inhibiting or potentiating an autoinhibited state or active state of an RTK. If, after testing, it is determined that the test compound does bind to the binding pocket, inhibits or enhances interactions of atomic contacts in a binding pocket, and/or inhibits or potentiates an autoinhibited or active state of an RTK, it is known as a "ligand".

The test compound may be designed or obtained from a library of compounds which may comprise peptides, as well as other compounds, such as small organic molecules and particularly new lead compounds. By way of example, the test compound may be a natural substance, a biological macromolecule, or an extract made from biological materials such as bacteria, fungi, or animal (particularly mammalian) cells or tissues, an organic or an inorganic molecule, a synthetic test compound, a semi-synthetic test compound, a carbohydrate, a monosaccharide, an oligosaccharide or polysaccharide, a glycolipid, a glycopeptide, a saponin, a heterocyclic compound, a structural or functional mimetic, a peptide, a peptidomimetic, a derivatised test compound, a peptide cleaved from a whole protein, or a peptide synthesised synthetically (such as, by way of example, either using a peptide synthesizer or by recombinant techniques or combinations thereof), a recombinant test compound, a natural or a non-natural test compound, a fusion protein or equivalent thereof and mutants, derivatives or combinations thereof.

The increasing availability of biomacromolecule structures of potential pharmacophoric molecules that have been solved crystallographically has prompted the development of a variety of direct computational methods for molecular design, in which the steric and electronic properties of substrate binding sites are use to guide the design of potential ligands (Cohen et al. (1990) *J. Med. Cam.* 33: 883-894; Kuntz et al. (1982) *J. Mol. Biol* 161: 269-288; DesJarlais (1988) *J. Med. Cam.* 31: 722-729; Bartlett

et al. (1989) (*Spec. Publ., Roy. Soc. Chem.*) 78: 182-196; Goodford et al. (1985) *J. Med. Cam.* 28: 849-857; DesJarlais et al. *J. Med. Cam.* 29: 2149-2153). Directed methods generally fall into two categories: (1) design by analogy in which 3-D structures of known molecules (such as from a crystallographic database) are docked to the receptor structure and scored for goodness-of-fit; and (2) *de novo* design, in which the ligand model is constructed piece-wise in the receptor. The latter approach, in particular, can facilitate the development of novel molecules, uniquely designed to bind to the subject receptor.

The test compound may be screened as part of a library or a data base of molecules. Modulators of inactivated/activated states of an RTK or binding pocket thereof may be identified by docking a computer representation of compounds from one or more data base of molecules. Data bases which may be used include ACD (Molecular Designs Limited), NCI (National Cancer Institute), CCDC (Cambridge Crystallographic Data Center), CAST (Chemical Abstract Service), Derwent (Derwent Information Limited), Maybridge (Maybridge Chemical Company Ltd), Aldrich (Aldrich Chemical Company), DOCK (University of California in San Francisco), and the Directory of Natural Products (Chapman & Hall). Computer programs such as CONCORD (Tripos Associates) or DB-Converter (Molecular Simulations Limited) can be used to convert a data set represented in two dimensions to one represented in three dimensions.

Test compounds may tested for their capacity to fit spatially into a binding pocket. As used herein, the term "fits spatially" means that the three-dimensional structure of the test compound is accommodated geometrically in a cavity of a binding pocket. The test compound can then be considered to be a ligand.

A favourable geometric fit occurs when the surface area of the test compound is in close proximity with the surface area of the cavity of a binding pocket without forming unfavorable interactions. A favourable complementary interaction occurs where the test compound interacts by hydrophobic, aromatic, ionic, dipolar, or hydrogen donating and accepting forces. Unfavourable interactions may be steric hindrance between atoms in the test compound and atoms in the binding pocket.

If a model of the present invention is a computer model, the test compounds may be positioned in a binding pocket through computational docking. If, on the other hand, the model of the present invention is a structural model, the test compounds may be positioned in the binding pocket by, for example, manual docking.

As used herein the term "docking" refers to a process of placing a compound in close proximity with a binding pocket, or a process of finding low energy conformations of a test compound/ binding pocket complex.

In an illustrative embodiment, the design of potential RTK, in particular EphB2 ligands begins from the general perspective of shape complimentarity for an active site and substrate specificity subsites of the receptor, and a search algorithm is employed which is capable of scanning a database of small molecules of known three-dimensional structure for candidates which fit geometrically into the target protein site. It is not expected that the molecules found in the shape search will necessarily be leads themselves, since no evaluation of chemical interaction need necessarily be made during the initial search.

Rather, it is anticipated that such candidates might act as the framework for further design, providing molecular skeletons to which appropriate atomic replacements can be made. Of course, the chemical complimentarity of these molecules can be evaluated, but it is expected that atom types will be changed to maximize the electrostatic, hydrogen bonding, and hydrophobic interactions with the receptor. Most algorithms of this type provide a method for finding a wide assortment of chemical structures that are complementary to the shape of a binding site of the subject receptor. Each of a set of small molecules from a particular data-base, such as the Cambridge Crystallographic Data Bank (CCDB) (Allen et al. (1973) *J. Chem. Doc.* 13: 119), is individually docked to the binding pocket or site of an RTK, in particular an EphB2 receptor, in a number of geometrically permissible orientations with use of a docking algorithm. In a preferred embodiment, a set of computer algorithms called DOCK, can be used to characterize the shape of invaginations and grooves that form active sites and recognition surfaces of a subject receptor (Kuntz et al. (1982) *J. Mol. Biol* 161: 269-288). The program can also search a database of small molecules for templates whose shapes are complementary to particular binding pockets or sites of a receptor (DesJarlais et al. (1988) *J Med Chem* 31: 722-729). These templates normally require modification to achieve good chemical and electrostatic interactions (DesJarlais et al. (1989) *ACS Symp Ser* 413: 60-69). However, the program has been shown to position accurately known cofactors for ligands based on shape constraints alone.

The orientations are evaluated for goodness-of-fit and the best are kept for further examination using molecular mechanics programs, such as AMBER or CHARMM. Such algorithms have previously proven successful in finding a variety of molecules that are complementary in shape to a given binding site of a receptor, and have been shown to have several attractive features. First, such algorithms can retrieve a remarkable diversity of molecular architectures. Second, the best structures have, in previous applications to other proteins, demonstrated impressive shape complementarity over an extended surface area. Third, the overall approach appears to be quite robust with respect to small uncertainties in positioning of the candidate atoms.

Goodford (1985, *J Med Chem* 28:849-857) and Boobbyer et al. (1989, *J Med Chem* 32:1083-1094) have produced a computer program (GRID) which seeks to determine regions of high affinity for different chemical groups (termed probes) on the molecular surface of the binding site. GRID hence provides a tool for suggesting modifications to known ligands that might enhance binding. It may be anticipated that some of the sites discerned by GRID as regions of high affinity correspond to "pharmacophoric patterns" determined inferentially from a series of known ligands. As used herein, a pharmacophoric pattern is a geometric arrangement of features of the anticipated ligand that is believed to be important for binding. Attempts have been made to use pharmacophoric patterns as a search screen for novel ligands (Jakes et al. (1987) *J Mol Graph* 5:41-48; Brint et al. (1987) *J Mol Graph* 5:49-56; Jakes et al. (1986) *J Mol Graph* 4:12-20); however, the constraint of steric and "chemical" fit in the putative (and possibly unknown) receptor binding pocket or site is ignored. Goodsell and Olson (1990, *Proteins: Struct Funct Genet* 8:195-202) have used the Metropolis (simulated annealing) algorithm to dock a single known ligand into a target protein. They allow torsional flexibility in the ligand and use GRID interaction energy

maps as rapid lookup tables for computing approximate interaction energies. Given the large number of degrees of freedom available to the ligand, the Metropolis algorithm is time-consuming and is unsuited to searching a candidate database of a few thousand small molecules.

Yet a further embodiment of the present invention utilizes a computer algorithm such as CLIX which searches such databases as CCDB for small molecules which can be oriented in a receptor binding pocket or site in a way that is both sterically acceptable and has a high likelihood of achieving favorable chemical interactions between the candidate molecule and the surrounding amino acid residues. The method is based on characterizing a binding pocket in terms of an ensemble of favorable binding positions for different chemical groups and then searching for orientations of the candidate molecules that cause maximum spatial coincidence of individual candidate chemical groups with members of the ensemble. The current availability of computer power dictates that a computer-based search for novel ligands follows a breadth-first strategy. A breadth-first strategy aims to reduce progressively the size of the potential candidate search space by the application of increasingly stringent criteria, as opposed to a depth-first strategy wherein a maximally detailed analysis of one candidate is performed before proceeding to the next. CLIX conforms to this strategy in that its analysis of binding is rudimentary -it seeks to satisfy the necessary conditions of steric fit and of having individual groups in "correct" places for bonding, without imposing the sufficient condition that favorable bonding interactions actually occur. A ranked "shortlist" of molecules, in their favored orientations, is produced which can then be examined on a molecule-by-molecule basis, using computer graphics and more sophisticated molecular modeling techniques. CLIX is also capable of suggesting changes to the substituent chemical groups of the candidate molecules that might enhance binding.

The algorithmic details of CLIX is described in Lawerence et al. (1992) *Proteins* 12:31-41, and the CLIX algorithm can be summarized as follows. The GRID program is used to determine discrete favorable interaction positions (termed target sites) in the binding pocket or site of the protein for a wide variety of representative chemical groups. For each candidate ligand in the CCDB an exhaustive attempt is made to make coincident, in a spatial sense in the binding site of the protein, a pair of the candidate's substituent chemical groups with a pair of corresponding favorable interaction sites proposed by GRID. All possible combinations of pairs of ligand groups with pairs of GRID sites are considered during this procedure. Upon locating such coincidence, the program rotates the candidate ligand about the two pairs of groups and checks for steric hindrance and coincidence of other candidate atomic groups with appropriate target sites. Particular candidate/orientation combinations that are good geometric fits in the binding site and show sufficient coincidence of atomic groups with GRID sites are retained.

Consistent with the breadth-first strategy, this approach involves simplifying assumptions. Rigid protein and small molecule geometry is maintained throughout. As a first approximation rigid geometry is acceptable as the energy minimized coordinates of an RTK, in particular an EphB2 deduced structure, as described herein, describe an energy minimum for the molecule, albeit a local one. If the surface residues of the site of interest are not involved in crystal contacts then the crystal configuration of those residues is used merely as a starting point for energy minimization, and potential solution structures for those residues

determined. The deduced structure described herein should reasonably mimic the mean solution configuration.

A further assumption implicit in CLIX is that the potential ligand, when introduced into the binding pocket or site of a receptor, does not induce change in the protein's stereochemistry or partial charge distribution and so alter the basis on which the GRID interaction energy maps were computed. It must also be stressed that the interaction sites predicted by GRID are used in a positional and type sense only, i.e., when a candidate atomic group is placed at a site predicted as favorable by GRID, no check is made to ensure that the bond geometry, the state of protonation, or the partial charge distribution favors a strong interaction between the protein and that group. Such detailed analysis should form part of more advanced modeling of candidates identified in the CLIX shortlist.

Yet another embodiment of a computer-assisted molecular design method for identifying ligands of a binding pocket of an RTK comprises the *de novo* synthesis of potential ligands by algorithmic connection of small molecular fragments that will exhibit the desired structural and electrostatic complementarity with an active site or binding pocket of the receptor. The methodology employs a large template set of small molecules with are iteratively pieced together in a model of an RTK active site or binding pocket. Each stage of ligand growth is evaluated according to a molecular mechanics-based energy function, which considers van der Waals and coulombic interactions, internal strain energy of the lengthening ligand, and desolvation of both ligand and receptor. The search space can be managed by use of a data tree which is kept under control by pruning according to the binding criteria.

In an illustrative embodiment, the search space is limited to consider only amino acids and amino acid analogs as the molecular building blocks. Such a methodology generally employs a large template set of amino acid conformations, though need not be restricted to just the 20 natural amino acids, as it can easily be extended to include other related fragments of interest to the medicinal chemist, e.g. amino acid analogs. The putative ligands that result from this construction method are peptides and peptide-like compounds rather than the small organic molecules that are typically the goal of drug design research. The appeal of the peptide building approach is not that peptides are preferable to organics as potential pharmaceutical agents, but rather that: (1) they can be generated relatively rapidly de novo; (2) their energetics can be studied by well-parameterized force field methods; (3) they are much easier to synthesize than are most organics; and (4) they can be used in a variety of ways, for peptidomimetic ligand design, protein-protein binding studies, and even as shape templates in the more commonly used 3D organic database search approach described above.

Such a *de novo* peptide design method has been incorporated in a software package called GROW (Moon et al. (1991) *Proteins* 11:314-328). In a typical design session, standard interactive graphical modeling methods are employed to define the structural environment in which GROW is to operate. For instance, environment could be an active site binding pocket of an RTK, in particular an EphB2, or it could be a set of features on the protein's surface to which the user wishes to bind a peptide-like molecule. The GROW program then operates to generate a set of potential ligand molecules. Interactive modeling

methods then come into play again, for examination of the resulting molecules, and for selection of one or more of them for further refinement.

To illustrate, GROW operates on an atomic coordinate file generated by the user in the interactive modeling session, such as the coordinates provided in Table 3, or the coordinates of a binding pocket or active site as described in Table 2 and 3 plus a small fragment (e.g., an acetyl group) positioned in the active site to provide a starting point for peptide growth. These are referred to as "site" atoms and "seed" atoms, respectively. A second file provided by the user contains a number of control parameters to guide the peptide growth (Moon et al. (1991) *Proteins* 11:314-328).

The operation of the GROW algorithm is conceptually fairly simple. GROW proceeds in an iterative fashion, to systematically attach to the seed fragment each amino acid template in a large preconstructed library of amino acid conformations. When a template has been attached, it is scored for goodness-of-fit to the receptor site or binding pocket, and then the next template in the library is attached to the seed. After all the templates have been tested, only the highest scoring ones are retained for the next level of growth. This procedure is repeated for the second growth level; each library template is attached in turn to each of the bonded seed/amino acid molecules that were retained from the first step, and is then scored. Again, only the best of the bonded seed/dipeptide molecules that result are retained for the third level of growth. The growth of peptides can proceed in the N-to-C direction only, the reverse direction only, or in alternating directions, depending on the initial control specifications supplied by the user. Successive growth levels therefore generate peptides that are lengthened by one residue. The procedure terminates when the user-defined peptide length has been reached, at which point the user can select from the constructed peptides those to be studied further. The resulting data provided by the GROW procedure includes not only residue sequences and scores, but also atomic coordinates of the peptides, related directly to the coordinate system of the receptor site atoms.

In yet another embodiment, potential pharmacophoric compounds can be determined using a method based on an energy minimization-quenched molecular dynamics algorithm for determining energetically favorable positions of functional groups in the binding pockets of the subject receptor. The method can aid in the design of molecules that incorporate such functional groups by modification of known ligands or *de novo* construction.

For example, the multiple copy simultaneous search method (MCSS) described by Miranker et al. (1991) *Proteins* 11: 29-34 may be employed. To determine and characterize a local minima of a functional group in the forcefield of the protein, multiple copies of selected functional groups are first distributed in a binding pocket of interest on the RTK protein. Energy minimization of these copies by molecular mechanics or quenched dynamics yields the distinct local minima. The neighborhood of these minima can then be explored by a grid search or by constrained minimization. In one embodiment, the MCSS method uses the classical time dependent Hartee (TDH) approximation to simultaneously minimize or quench many identical groups in the forcefield of the protein.

Implementation of the MCSS algorithm requires a choice of functional groups and a molecular mechanics model for each of them. Groups must be simple enough to be easily characterized and

manipulated (3-6 atoms, few or no dihedral degrees of freedom), yet complex enough to approximate the steric and electrostatic interactions that the functional group would have in binding to the pocket or site of interest in the RTK protein. A preferred set is, for example, one in which most organic molecules can be described as a collection of such groups (*Patai's Guide to the Chemistry of Functional Groups*, ed. S. Patai (New York: John Wiley, and Sons, (1989)). This includes fragments such as acetonitrile, methanol, acetate, methyl ammonium, dimethyl ether, methane, and acetaldehyde.

Determination of the local energy minima in the binding pocket or site requires that many starting positions be sampled. This can be achieved by distributing, for example, 1,000-5,000 groups at random inside a sphere centered on the binding site; only the space not occupied by the protein needs to be considered. If the interaction energy of a particular group at a certain location with the protein is more positive than a given cut-off (e.g. 5.0 kcal/mole) the group is discarded from that site. Given the set of starting positions, all the fragments are minimized simultaneously by use of the TDH approximation (Elber et al. (1990) *J Am Chem Soc* 112: 9161-9175). In this method, the forces on each fragment consist of its internal forces and those due to the protein. The essential element of this method is that the interactions between the fragments are omitted and the forces on the protein are normalized to those due to a single fragment. In this way simultaneous minimization or dynamics of any number of functional groups in the field of a single protein can be performed.

Minimization is performed successively on subsets of, for example 100, of the randomly placed groups. After a certain number of step intervals, such as 1,000 intervals, the results can be examined to eliminate groups converging to the same minimum. This process is repeated until minimization is complete (e.g. RMS gradient of 0.01 kcal/mole/C). Thus the resulting energy minimized set of molecules comprises what amounts to a set of disconnected fragments in three dimensions representing potential pharmacophores.

The next step then is to connect the pharmacophoric pieces with spacers assembled from small chemical entities (atoms, chains, or ring moieties). In a preferred embodiment, each of the disconnected can be linked in space to generate a single molecule using such computer programs as, for example, NEWLEAD (Tschinke et al. (1993) *J Med Chem* 36: 3863,3870). The procedure adopted by NEWLEAD executes the following sequence of commands (1) connect two isolated moieties, (2) retain the intermediate solutions for further processing, (3) repeat the above steps for each of the intermediate solutions until no disconnected units are found, and (4) output the final solutions, each of which is a single molecule. Such a program can use for example, three types of spacers: library spacers, single-atom spacers, and fuse-ring spacers. The library spacers are optimized structures of small molecules such as ethylene, benzene and methylamide. The output produced by programs such as NEWLEAD consist of a set of molecules containing the original fragments now connected by spacers. The atoms belonging to the input fragments maintain their original orientations in space. The molecules are chemically plausible because of the simple makeup of the spacers and functional groups, and energetically acceptable because of the rejection of solutions with van-der Waals radii violations.

A screening method of the present invention may comprise the following steps:

(i) generating a computer model of a binding pocket using a crystal according to the invention;

(ii) docking a computer representation of a test compound with the computer model;

(iii) analysing the fit of the compound in the binding pocket.

In an aspect of the invention, a method is provided comprising the following steps:

(a) docking a computer representation of a structure of a test compound into a computer representation of a binding pocket of an RTK defined in accordance with the invention using a computer program, or by interactively moving the representation of the test compound into the representation of the binding pocket;

(b) characterizing the geometry and the complementary interactions formed between the atoms of the binding pocket and the compound; optionally

(c) searching libraries for molecular fragments which can fit into the empty space between the compound and the binding pocket and can be linked to the compound; and

(d) linking the fragments found in (c) to the compound and evaluating the new modified compound.

In an embodiment of the invention, a method is provided which comprises the following steps:

(a) docking a computer representation of a test compound from a computer data base with a computer representation of a selected binding pocket on an RTK defined in accordance with the invention to define a complex;

(b) determining a conformation of the complex with a favorable fit and favourable complementary interactions; and

(c) identifying test compounds that best fit the selected binding pocket as potential modulators of the RTK.

In another embodiment of the invention, a method is provided which comprises docking a computer representation of a selected binding pocket of an RTK defined by the atomic interactions, atomic contacts, or structural coordinates in accordance with the invention to define a complex. In particular a method is provided comprising:

(a) docking a computer representation of a test compound from a computer database with a computer representation of a selected binding pocket of an RTK defined by the atomic interactions, atomic contacts, or structural coordinates described herein;

(b) determining a conformation of the complex with a favorable fit and favourable complementary interactions; and

(c) identifying test compounds that best fit the selected binding pocket as potential modulators of the RTK.

A model used in a screening method may comprise a binding pocket either alone or in association with one or more ligands and/or cofactors. For example, the model may comprise the binding pocket in association with a nucleotide (or analogue thereof), a substrate (or analogue thereof), and/or modulator.

If the model comprises an unassociated binding pocket, then the selected site under investigation may be the binding pocket itself. The test compound may, for example, mimic a known ligand (e.g. nucleotide or substrate) for an RTK in order to interact with the binding pocket. The selected site may alternatively be another site on the RTK.

If the model comprises an associated binding pocket, for example a binding pocket in association with a ligand, the selected site may be the binding pocket or a site made up of the binding pocket and the complexed ligand, or a site on the ligand itself. The test compound may be investigated for its capacity to modulate the interaction with the associated molecule.

The screening methods described herein may be applied to a plurality of test compounds, to identify those that best fit the selected site. The screening methods may be used to identify a modulator that changes an autoinhibited state of an RTK to an active state, or an active state to an autoinhibited state.

A test compound (or plurality of test compounds) may be selected on the basis of their similarity to a known ligand for an RTK, in particular an Eph receptor. For example, the screening method may comprise the following steps:

(i) generating a computer model of a binding pocket in complex with a ligand;

(ii) searching for a test compound with a similar three dimensional structure and/or similar chemical groups as the ligand; and

(iii) evaluating the fit of the test compound in the binding pocket.

Searching may be carried out using a database of computer representations of potential compounds, using methods known in the art.

The present invention also provides a method for designing ligands for RTKs. It is well known in the art to use a screening method as described above to identify a test compound with promising fit, but then to use this test compound as a starting point to design a ligand with improved fit to the model. Such techniques are known as "structure–based ligand design" (See Kuntz et al., 1994, Acc. Chem. Res. 27:117; Guida, 1994, Current Opinion in Struc. Biol. 4: 777; and Colman, 1994, Current Opinion in Struc. Biol. 4: 868, for reviews of structure-based drug design and identification;and Kuntz et al 1982, J. Mol. Biol. 162:269; Kuntz et al., 1994, Acc. Chem. Res. 27: 117; Meng et al., 1992, J. Compt. Chem. 13: 505; Bohm, 1994, J. Comp. Aided Molec. Design 8: 623 for methods of structure-based modulator design).

Examples of computer programs that may be used for structure-based ligand design are CAVEAT (Bartlett et al., 1989, in "Chemical and Biological Problems in Molecular Recognition", Roberts, S.M. Ley, S.V.; Campbell, N.M. eds; Royal Society of Chemistry: Cambridge, pp 182-196); FLOG (Miller et al., 1994, J. Comp. Aided Molec. Design 8:153); PRO Modulator (Clark et al., 1995 J. Comp. Aided Molec. Design 9:13); MCSS (Miranker and Karplus, 1991, Proteins: Structure, Fuction, and Genetics 8:195); and, GRID (Goodford, 1985, J. Med. Chem. 28:849).

The method may comprise the following steps:

(i) docking a model of a test compound with a model of a binding pocket;

(ii) identifying one or more groups on the test compound which may be modified to improve their fit in the binding pocket;

(iii) replacing one or more identified groups to produce a modified test compound model; and

(iv) docking the modified test compound model with the model of the binding pocket.

Evaluation of fit may comprise the following steps:

(a) mapping chemical features of a test compound such as by hydrogen bond donors or acceptors, hydrophobic/lipophilic sites, positively ionizable sites, or negatively ionizable sites; and

(b) adding geometric constraints to selected mapped features.

The fit of the modified test compound may then be evaluated using the same criteria.

The chemical modification of a group may either enhance or reduce hydrogen bonding interaction, charge interaction, hydrophobic interaction, Van Der Waals interaction or dipole interaction between the test compound and the key amino acid residue(s) of the binding pocket. Preferably the group modifications involve the addition removal or replacement of substituents onto the test compound such that the substituents are positioned to collide or to bind preferentially with one or more amino acid residues that correspond to the key amino acid residues of the binding pocket.

If a modified test compound model has an improved fit, then it may bind to a binding pocket and be considered to be a "ligand". Rational modification of groups may be made with the aid of libraries of molecular fragments which may be screened for their capacity to fit into the available space and to interact with the appropriate atoms. Databases of computer representations of libraries of chemical groups are available commercially, for this purpose.

The test compound may also be modified "*in situ*" (i.e. once docked into the potential binding pocket), enabling immediate evaluation of the effect of replacing selected groups. The computer representation of the test compound may be modified by deleting a chemical group or groups, or by adding a chemical group or groups. After each modification to a compound, the atoms of the modified compound and potential binding pocket can be shifted in conformation and the distance between the modulator and the binding pocket atoms may be scored on the basis of geometric fit and favourable complementary interactions between the molecules. This technique is described in detail in Molecular Simulations User Manual, 1995 in LUDI.

Examples of ligand building and/or searching computer programs include programs in the Molecular Simulations Package (Catalyst), ISIS/HOST, ISIS/BASE, and ISIS/DRAW (Molecular Designs Limited), and UNITY (Tripos Associates).

The "starting point" for rational ligand design may be a known ligand for the enzyme. For example, in order to identify potential modulators of an RTK, in particular an Eph receptor, a logical approach would be to start with a known ligand (for example a nucleotide or known kinase inhibitors) to produce a molecule which mimics the binding of the ligand. Such a molecule may, for example, act as a competitive inhibitor for the true ligand, or may bind so strongly that the interaction (and inhibition) is effectively irreversible.

Such a method may comprise the following steps:

(i) generating a computer model of a binding pocket in complex with a ligand;

(ii) replacing one or more groups on the ligand model to produce a modified ligand; and

(iii) evaluating the fit of the modified ligand in the binding pocket.

The replacement groups could be selected and replaced using a compound construction program which replaces computer representations of chemical groups with groups from a computer database, where the representations of the compounds are defined by structural coordinates.

In an embodiment, a screening method is provided for identifying a ligand of an RTK, in particular an Eph receptor, comprising the step of using the structural coordinates of a nucleotide or component thereof, defined in relation to its spatial association with a binding pocket of the invention, to generate a compound that is capable of associating with the binding pocket.

In an embodiment of the invention, a screening method is provided for identifying a ligand of an RTK, in particular an Eph receptor, comprising the step of using the structural coordinates of adenosine adenine, or ATP listed in Table 3 to generate a compound for associating with a binding pocket of RTK, in particular an Eph receptor as described herein. The following steps are employed in a particular method of the invention: (a) generating a computer representation of adenosine adenine, or ATP, defined by its structural coordinates listed in Table 3; (b) searching for molecules in a data base that are structurally or chemically similar to the defined adenosine adenine, or ATP, using a searching computer program, or replacing portions of the adenosine adenine, or ATP with similar chemical structures from a database using a compound building computer program.

A screening method is provided for identifying a ligand of an RTK, in particular an Eph receptor, comprising the step of using the structural coordinates of a binding pocket comprising a juxtamembrane region or part thereof listed in Table 3 to generate a compound for associating with a kinase domain of an RTK, in particular an Eph receptor. The following steps are employed in a particular method of the invention: (a) generating a computer representation of a binding pocket comprising a juxtamembrane region or part thereof defined by its structural coordinates listed in Table 3; and (b) searching for molecules in a data base that are structurally or chemically similar to the defined binding pocket using a searching computer program, or replacing portions of the binding pocket with structures from a database using a compound building computer program.

The screening methods of the present invention may be used to identify compounds or entities that associate with a molecule that associates with an RTK, in particular an Eph receptor (for example, a nucleotide).

Compounds and entities (e.g. ligands) of RTKs, in particular Eph receptors, identified using the above-described methods may be prepared using methods described in standard reference sources utilized by those skilled in the art. For example, organic compounds may be prepared by organic synthetic methods described in references such as March, 1994, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, New York, McGraw Hill.

Test compounds and ligands which are identified using a crystal or model of the present invention can be screened in assays such as those well known in the art. Screening may be for example *in vitro*, in cell culture, and/or *in vivo*. Biological screening assays preferably centre on activity-based response

models, binding assays (which measure how well a compound binds to a binding pocket of a receptor), and bacterial, yeast, and animal cell lines (which measure the biological effect of a compound in a cell). The assays may be automated for high throughput screening in which large numbers of compounds can be tested to identify compounds with the desired activity. The biological assay may also be an assay for the binding activity of a compound that selectively binds to the binding pocket compared to other receptors.

LIGANDS/COMPOUNDS IDENTIFIED BY SCREENING METHODS

The present invention provides a ligand or compound identified by a screening method of the present invention. A ligand or compound may have been designed rationally by using a model according to the present invention. A ligand or compound identified using the screening methods of the invention may specifically associate with a target compound, or part thereof (e.g. a binding pocket). In the present invention the target compound may be the RTK (e.g. Eph receptor) or part thereof, or a molecule that is capable of associating with the RTK or part thereof (for example a nucleotide). In an embodiment, the ligand is capable of binding to phosphoregulatory sites of a binding pocket, in particular phosphoregulatory sites of a juxtamembrane region or kinase domain. In another embodiment, the ligand is capable of binding to the activation segment of a kinase domain of an Eph receptor.

A ligand or compound identified using a screening method of the invention may act as a "modulator", i.e. a compound which affects the activity of an RTK in particular an Eph receptor. A modulator may reduce, enhance or alter the biological function of an RTK, in particular an Eph receptor. For example a modulator may modulate the capacity of the RTK to autophosphorylate. An alteration in biological function may be characterised by a change in specificity. For example, a modulator may cause the RTK to accept a different nucleotide, to phosphorylate a different amino acid residue, or to work with a different metal cofactor. A modulator may dispose an RTK to favor the autoinhibited state or active state. In order to exert its function, the modulator commonly binds to a binding pocket.

A "modulator" which is capable of reducing the biological function of the enzyme may also be known as an inhibitor. Preferably an inhibitor reduces or blocks the capacity of the enzyme to autophosphorylate. An inhibitor may promote the autoinhibition state of an RTK. The inhibitor may mimic the binding of a nucleotide or substrate, for example, it may be a nucleotide or substrate analogue. A nucleotide analogue may be designed by considering the interactions between the nucleotide and the RTK (for example, by using information derivable from the crystal of the invention) and specifically altering one or more groups (as described above).

The present invention also provides a method for modulating the activity of an RTK, in particular an Eph receptor, using a modulator according to the present invention. The invention also provides a method for inhibiting autophosphorylation of an RTK, preferably an Eph receptor, by potentiating the autoinhibition state of an RTK, or inhiting the active state of the RTK. Inhibition of phosphorylation of an RTK may decrease signaling by the RTK and inhibit cellular processes that may be involved in disease. It would be possible to monitor receptor activity following such treatments by a number of methods known in the art.

A modulator may be an agonist, partial agonist, partial inverse agonist or antagonist of an RTK.

As used herein, the term "agonist" means any ligand, which is capable of binding to a binding pocket and which is capable of increasing a proportion of the receptor that is in an active form, resulting in an increased biological response. The term includes partial agonists and inverse agonists.

As used herein, the term "partial agonist" means an agonist that is unable to evoke the maximal response of a biological system, even at a concentration sufficient to saturate the specific receptors.

As used herein, the term "partial inverse agonist" is an inverse agonist that evokes a submaximal response to a biological system, even at a concentration sufficient to saturate the specific receptors. At high concentrations, it will diminish the actions of a full inverse agonist.

As used herein, the term "antagonist" means any agent that reduces the action of another agent, such as an agonist. The antagonist may act at the same site as the agonist (competitive antagonism). The antagonistic action may result from a combination of the substance being antagonised (chemical antagonism) or the production of an opposite effect through a different receptor (functional antagonism or physiological antagonism) or as a consequence of competition for the binding site of an intermediate that links receptor activation to the effect observed (indirect antagonism).

As used herein, the term "competitive antagonism" refers to the competition between an agonist and an antagonist for a binding pocket of a receptor that occurs when the binding of agonist and antagonist becomes mutually exclusive. This may be because the agonist and antagonist compete for the same binding sites or pockets, or combine with adjacent but overlapping sites. A third possibility is that different sites are involved but that they influence the receptor macromolecules in such a way that agonist and antagonist molecules cannot be bound at the same time. If the agonist and antagonist form only short lived combinations with a binding pocket of a receptor so that equilibrium between agonist, antagonist and receptor is reached during the presence of the agonist, the antagonism will be surmountable over a wide range of concentrations. In contrast, some antagonists, when in close enough proximity to their binding site, may form a stable covalent bond with it and the antagonism becomes insurmountable when no spare receptors remain.

As mentioned above, an identified ligand or compound may act as a ligand model (for example, a template) for the development of other compounds. A modulator may be a mimetic of a ligand.

Like the test compound (see above) a modulator may be one or a variety of different sorts of molecule.(See examples herein.) A modulator may be an endogenous physiological compound, or it may be a natural or synthetic compound. The modulators of the present invention may be natural or synthetic. The term "modulator" also refers to a chemically modified ligand or compound.

The technique suitable for preparing a modulator will depend on its chemical nature. For example, peptides can be synthesized by solid phase techniques (Roberge JY *et al* (1995) Science 269: 202-204) and automated synthesis may be achieved, for example, using the ABI 43 1 A Peptide Synthesizer (Perkin Elmer) in accordance with the instructions provided by the manufacturer. Once cleaved from the resin, the peptide may be purified by preparative high performance liquid chromatography (e.g., Creighton (1983) Proteins Structures and Molecular Principles, WH Freeman and Co, New York NY). The composition of

the synthetic peptides may be confirmed by amino acid analysis or sequencing (e.g., the Edman degradation procedure; Creighton, *supra*).

If a modulator is a nucleotide, or a polypeptide expressable therefrom, it may be synthesized, in whole or in part, using chemical methods well known in the art (see Caruthers MH *et al* (1980) Nuc Acids Res Symp Ser 215-23, Horn T *et al* (1980) Nuc Acids Res Symp Ser 225-232), or it may be prepared using recombinant techniques well known in the art.

Organic compounds may be prepared by organic synthetic methods described in references such as March, 1994, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, New York, McGraw Hill.

The invention also relates to classes of modulators of RTKs based on the structure and shape of a nucleotide, or component thereof, or a substrate or component thereof, defined in relation to the nucleotide's or substrate's spatial association with a crystal structure of the invention or part thereof.

A class of modulators may comprise a compound containing a structure of adenine, adenosine, ribose, pyrophosphate, or ATP, and having one or more, preferably all, of the structural coordinates of adenine, adenosine, ribose, pyrophosphate, or ATP of Table 4. Functional groups in the adenine, adenosine, ribose, pyrophosphate, or ATP modulators may be substituted with, for example, alkyl, alkoxy, hydroxyl, aryl, cycloalkyl, alkenyl, alkynyl, thiol, thioalkyl, thioaryl, amino, or halo, or they may be modified using techniques known in the art.

Another class of modulators defined by the invention are compounds comprising an adenine triphosphate group having the structural coordinates of adenine triphosphate in the active site binding pocket of an Eph receptor.

The invention contemplates all optical isomers and racemic forms of the modulators of the invention.

PHARMACEUTICAL COMPOSITION

The present invention also provides for the use of a modulator according to the invention, in the manufacture of a medicament to treat and/or prevent a disease in a mammalian patient. There is also provided a pharmaceutical composition comprising such a modulator and a method of treating and/or preventing a disease comprising the step of administering such a modulator or pharmaceutical composition to a subject, preferably a mammalian patient.

The pharmaceutical compositions may be for human or animal usage in human and veterinary medicine and will typically comprise a pharmaceutically acceptable carrier, diluent, excipient, adjuvant or combination thereof.

Acceptable carriers or diluents for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remington's Pharmaceutical Sciences, Mack Publishing Co. (A. R. Gennaro edit. 1985). The choice of pharmaceutical carrier, excipient or diluent can be selected with regard to the intended route of administration and standard pharmaceutical practice. The pharmaceutical compositions may comprise as - or in addition to - the carrier, excipient or diluent any suitable binder(s), lubricant(s), suspending agent(s), coating agent(s), solubilising agent(s).

Preservatives, stabilizers, dyes and even flavouring agents may be provided in the pharmaceutical composition. Examples of preservatives include sodium benzoate, sorbic acid and esters of p-hydroxybenzoic acid. Antioxidants and suspending agents may also be used.

The routes for administration (delivery) include, but are not limited to, one or more of: oral (e.g. as a tablet, capsule, or as an ingestable solution), topical, mucosal (e.g. as a nasal spray or aerosol for inhalation), nasal, parenteral (e.g. by an injectable form), gastrointestinal, intraspinal, intraperitoneal, intramuscular, intravenous, intrauterine, intraocular, intradermal, intracranial, intratracheal, intravaginal, intracerebroventricular, intracerebral, subcutaneous, ophthalmic (including intravitreal or intracameral), transdermal, rectal, buccal, vaginal, epidural, sublingual.

Where the pharmaceutical composition is to be delivered mucosally through the gastrointestinal mucosa, it should be able to remain stable during transit though the gastrointestinal tract; for example, it should be resistant to proteolytic degradation, stable at acid pH and resistant to the detergent effects of bile.

Where appropriate, the pharmaceutical compositions can be administered by inhalation, in the form of a suppository or pessary, topically in the form of a lotion, gel, hydrogel, solution, cream, ointment or dusting powder, by use of a skin patch, orally in the form of tablets containing excipients such as starch or lactose or chalk, or in capsules or ovules either alone or in admixture with excipients, or in the form of elixirs, solutions or suspensions containing flavouring or colouring agents, or they can be injected parenterally, for example intravenously, intramuscularly or subcutaneously. For parenteral administration, the compositions may be best used in the form of a sterile aqueous solution which may contain other substances, for example enough salts or monosaccharides to make the solution isotonic with blood. The aqueous solutions should be suitably buffered (preferably to a pH of from 3 to 9), if necessary. The preparation of suitable parenteral formulations under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

If the agent of the present invention is administered parenterally, then examples of such administration include one or more of: intravenously, intra-arterially, intraperitoneally, intrathecally, intraventricularly, intraurethrally, intrasternally, intracranially, intramuscularly or subcutaneously administering the agent; and/or by using infusion techniques.

For buccal or sublingual administration the compositions may be administered in the form of tablets or lozenges which can be formulated in a conventional manner.

The tablets may contain excipients such as microcrystalline cellulose, lactose, sodium citrate, calcium carbonate, dibasic calcium phosphate and glycine, disintegrants such as starch (preferably corn, potato or tapioca starch), sodium starch glycollate, croscarmellose sodium and certain complex silicates, and granulation binders such as polyvinylpyrrolidone, hydroxypropylmethylcellulose (HPMC), hydroxypropylcellulose (HPC), sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, stearic acid, glyceryl behenate and talc may be included.

Solid compositions of a similar type may also be employed as fillers in gelatin capsules. Preferred excipients in this regard include lactose, starch, cellulose, milk sugar or high molecular weight polyethylene glycols. For aqueous suspensions and/or elixirs, the agent may be combined with various

sweetening or flavouring agents, colouring matter or dyes, with emulsifying and/or suspending agents and with diluents such as water, ethanol, propylene glycol and glycerin, and combinations thereof.

As indicated, a therapeutic agent (e.g. modulator) of the present invention can be administered intranasally or by inhalation and is conveniently delivered in the form of a dry powder inhaler or an aerosol spray presentation from a pressurised container, pump, spray or nebuliser with the use of a suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, a hydrofluoroalkane such as 1,1,1,2-tetrafluoroethane (HFA 134A™) or 1,1,1,2,3,3,3-heptafluoropropane (HFA 227EA™), carbon dioxide or other suitable gas. In the case of a pressurised aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. The pressurised container, pump, spray or nebuliser may contain a solution or suspension of the active compound, e.g. using a mixture of ethanol and the propellant as the solvent, which may additionally contain a lubricant, e.g. sorbitan trioleate. Capsules and cartridges (made, for example, from gelatin) for use in an inhaler or insufflator may be formulated to contain a powder mix of the agent and a suitable powder base such as lactose or starch.

Therapeutic administration of polypeptide modulators may also be accomplished using gene therapy. A nucleic acid including a promoter operatively linked to a heterologous polypeptide may be used to produce high-level expression of the polypeptide in cells transfected with the nucleic acid. DNA or isolated nucleic acids may be introduced into cells of a subject by conventional nucleic acid delivery systems. Suitable delivery systems include liposomes, naked DNA, and receptor-mediated delivery systems, and viral vectors such as retroviruses, herpes viruses, and adenoviruses.

APPLICATIONS

The invention provides a method for inhibiting kinase activity of an RTK comprising maintaining the RTK or a binding pocket thereof involved in regulating the kinase domain in an autoinhibited state, or potentiating an autoinhibited state for the RTK or binding pocket thereof involved in regulating the kinase domain. An autoinhibited state may be maintained or potentiated by inhibiting phosphorylation of phosphoregulatory sites of the juxtamembrane segment and/or kinase domain (e.g. activation segment). Inhibition may be accomplished using modulators, or altering the structure of a binding pocket of the RTK comprising the phosphoregulatory sites, to prevent phosphorylation of the sites.

The invention contemplates a method for altering the stability of an autoinhibited state of an RTK comprising phosphorylating phosphoregulatory sites of a juxtamembrane region of the RTK.

In an aspect the invention relates to a method for changing an RTK from an autoinhibited state to an active state comprising phosphorylating phosphoregulatory sites of a juxtamembrane region of the RTK.

In another aspect the invention provides a method for activating kinase activity of an RTK comprising phosphorylating phosphoregulatory sites of a juxtamembrane region and kinase domain (e.g. activation segment) of the RTK.

The invention further provides a method of treating a mammal, the method comprising administering to a mammal a modulator or pharmaceutical composition of the present invention.

In particular, the invention contemplates a method of treating or preventing a condition or disease associated with an RTK in a cellular organism, comprising:

(c) administering a modulator of the invention in an acceptable pharmaceutical preparation; and

(d) activating or inhibiting the RTK to treat or prevent the disease.

In an aspect the invention provides a method for treating or preventing a condition or disease involving increased RTK activity comprising maintaining the RTK or a binding pocket thereof involved in regulating the kinase domain of the RTK in an autoinhibited state. An autoinhibited state may be maintained as described herein. In an embodiment the condition or disease is cancer.

The invention provides for the use of a modulator identified by the methods of the invention in the preparation of a medicament to treat or prevent a disease in a cellular organism. Use of modulators of the invention to manufacture a medicament is also provided.

Typically, a physician will determine the actual dosage of a modulator or pharmaceutical composition of the invention that will be most suitable for an individual subject and it will vary with the age, weight and response of the particular patient and severity of the condition. There can, of course, be individual instances where higher or lower dosage ranges are merited.

The specific dose level and frequency of dosage for any particular patient may be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the age, body weight, general health, sex, diet, mode and time of administration, rate of excretion, drug combination, the severity of the particular condition, and the individual undergoing therapy. By way of example, the pharmaceutical composition of the present invention may be administered in accordance with a regimen of 1 to 10 times per day, such as once or twice per day.

For oral and parenteral administration to human patients, the daily dosage level of the agent may be in single or divided doses.

The modulators and compositions of the invention may be useful in the prevention and treatment of conditions involving aberrant RTKs.

Conditions which may be prevented or treated in accordance with the invention include but are not limited to lymphoproliferative conditions, malignant and pre-malignant conditions, arthritis, inflammation, and autoimmune disorders. Malignant and pre-malignant conditions may include solid tumors, B cell lymphomas, chronic lymphocytic leukemia, chronic myelogenous leukemia, prostate hypertrophy, Hirschsprung disease, glioblastoma, breast and ovarian cancer, adenocarcinoma of the salivary gland, premyelocytic leukemia, prostate cancer, multiple endocrine neoplasia type IIA and IIB, medullary thyroid carcinoma, papillary carcinoma, papillary renal carcinoma, hepatocellular carcinoma, gastrointestinal stromal tumors, sporadic mastocytosis, acute myeloid leukemia, large cell lymphoma or Alk lymphoma, chronic myeloid leukemia, hematological /solid tumors, papillary thyroid carcinoma, stem cell leukemia/lymphoma syndrome, acute myelogenous leukemia, osteosarcoma, multiple myeloma, preneoplastic liver foci, and resistance to chemotherapy. Diseases associated with increased cell survival, or the inhibition of apoptosis, include cancers (e.g. follicular lymphomas, carcinomas with p53 mutations, hormone-dependent tumors such as breast cancer, prostate cancer, Kaposi's sarcoma and ovarian cancer); autoimmune disorders (such as lupus erythematosus and immune-related glomerulonephritis rheumatoid

arthritis) and viral infections (such as herpes viruses, pox viruses, and adenoviruses); inflammation, graft vs. host disease, acute graft rejection and chronic graft rejection.

Eph receptors and ephrins mediate contact-dependent repulsive guidance of migrating cells and axons in culture and *in vivo*. Many Eph family members are prominently expressed in the developing nervous system, and ephrin stimulation of growing primary axons *in vitro* results in axonal retraction or repulsion, characterized by a collapse of actin-rich growth cone structures at the leading edge of the cell. Mice bearing homozygous null mutations in EphA8 or in both EphB2 and EphB3 exhibit abnormal migration of axon tracts in the brain. Ephrin-induced retraction of exploratory actin filopodia has also been described *in vivo* in migrating Eph receptor-expressing neural crest cells.

The Eph receptors and ephrins have also been implicated in cell sorting and boundary formation. Eph-receptor signaling is able to modulate both cell-cell and cell-substrate attachment. Bidirectional Eph receptor-ephrin signaling is important for the formation of boundaries between rhombomeres of the hind brain. These cellular responses to Eph receptor stimulation indicate that they may regulate signaling events which control cytoskeletal architecture and cell adhesion functions.

Therefore, modulators of Eph receptors may be used to modulate axonogenesis, nerve cell interactions and regeneration, to treat conditions such as neurodegenerative diseases and conditions involving trauma and injury to the nervous system, for example Alzheimer's disease, Parkinson's disease, Huntington's disease, demylinating diseases, such as multiple sclerosis, amyotrophic lateral sclerosis, bacterial and viral infections of the nervous system, deficiency diseases, such as Wernicke's disease and nutritional polyneuropathy, progressive supranuclear palsy, Shy Drager's syndrome, multistem degeneration and olivo ponto cerebellar atrophy, peripheral nerve damage, trauma and ischemia resulting from stroke.

Therapeutic efficacy and toxicity of compositions and modulators of the invention may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such as by calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The therapeutic index is the dose ratio of therapeutic to toxic effects and it can be expressed as the ED_{50}/LD_{50} ratio. Pharmaceutical compositions that exhibit large therapeutic indices are preferred.

The invention will now be illustrated by the following non-limiting example:

EXAMPLE:

The following methods were used in the investigation described in the example:

Methods

Protein Expression and Purification

Mutagenesis of the juxtamembrane tyrosines (Y604/610F) of murine EphB2 was performed using a PCR-based approach. The amplified cDNA sequence, corresponding to the receptor's juxtamembrane region and kinase domain (residues 595-906), was cloned into pGEX-4T-1 (Pharmacia). The glutathione-S transferase (GST)-EphB2 construct was transformed into *Escherichia coli* B834 cells and the cells grown in minimal media supplemented with selenomethionine, with overnight induction at 15°C, and 0.15

mM IPTG (isopropyl-β-D-thiogalactopyranoside, BioShop). Cells were lysed by homogenization and sonication in 25 mM HEPES (pH 7.5), 50 mM NaCl, 20% glycerol, 2 mM DTT, 2mM phenyl-methyl sulphonyl fluoride. Purification of the selenomethionyl derivative of EphB2 was performed as previously described (Binns et al., 2000), with the exception that the buffer used for gel filtration (buffer C) was 10 mM HEPES (pH 7.5), 50 mM NaCl, 1 mM DTT.

Crystallization, Data Collection, and Structure Determination

Hanging drops containing 1 µl of 12.5 mg/ml protein in buffer C were mixed with equal volumes of reservoir buffer containing 0.1 M HEPES (pH 7.0), 0.2 M magnesium chloride, 10% (w/v) PEG 4000, 10% (v/v) isopropanol, and 15% (v/v) ethylene glycol. Rod-like crystals were obtained overnight at 28°C after streak seeding with smaller crystals obtained initially. The crystals belong to primitive space group $P2_1$, (a = 47.86 Å, b = 98.09 Å, c = 68.18 Å, $\alpha = \gamma = 90°$, $\beta = 104.97°$), with two molecules of EphB2 in the asymmetric unit. Crystals were flash frozen by immersion in liquid nitrogen. A MAD experiment was performed on a frozen crystal at APS beamline BM 14-D ($\lambda1$ = 0.9790 Å, $\lambda2$ = 0.9788 Å, $\lambda3$ = 0.9770 Å) using a Quantum 4 ADSC CCD detector. Data processing and reduction was carried out with the HKL program suite (Otwinowski and Minor, 1997). The programs SHARP (La Fortelle and Bricogne, 1997) and SnB (Miller et al., 1994) were used in combination to locate and subsequently refine positions for 22 of the possible 30 Se sites. Following density modification with Solomon (Abrahams and Leslie, 1996), a partial model was generated using O (Jones et al., 1991) and refined using CNS (Brunger et al., 1998) (R-factors > 40%). Consequently, crystals of EphB2 in complex with 2 µM AMP-PNP were grown as described above (space group - P1, a = 47.05 Å, b = 57.62 Å, c = 67.74 Å, α = 112.95°, β = 103.17°, γ = 91.58°), with two molecules per asymmetric unit. Diffraction data was collected to 1.9 Å at APS beamline BM 14-C (λ = 1.00 Å) using a Quantum 4 ADSC CCD detector and processed with the HKL program suite. Molecular replacement solutions were determined with AMoRe (Navaza, 1994; CCP4, 1994), using one monomer of the $P2_1$-derived model as a search molecule. The two AMoRe solutions, which correspond to the two EphB2 molecules in the asymmetric unit, refined readily in CNS. With minimal modification to the starting model, the model has been refined to a working R value of 24.1% and a free R value of 27.7%. As defined in PROCHECK (Laskowski et al., 1993), 90.8 % of protein residues are in the most favored regions of the Ramachandran plot, with none in the disallowed regions. Pertinent statistics for data collection and refinement are shown in Table 1.

Mutagenesis

The cDNA sequence of the juxtamembrane region and kinase domain of murine EphA4 (amino acids 591-896), corresponding to residues 599-906 of murine EphB2, was cloned into pGEX-4T-2 (Pharmacia). The murine EphB2 numbering scheme was employed, and the corresponding EphA4 residue numbers are listed in parentheses. Using a PCR-based approach, Tyr 604 (Tyr596) and Tyr 610 (Tyr602) were mutated to phenylalanine. The following site-directed mutants were then generated using this doubly mutated construct: (1) ΔJX_{all}; deletion of 599-621 (591-613), (2) ΔJX1; deletion of 599-606 (591-598), (3) ΔJX1+2; deletion of 599-610 (591-602), (4) Pro607Gly (Pro599Gly), (5) Phe608Asp (Phe600Asp), (6) Phe620Asp (Phe612Asp), (7) Ser680Trp (Ser672Trp), (8) ΔJX1+2 plus Phe620Asp, and (9)

Tyr604/610Glu (Tyr596/602Glu). The GST-EphA4 constructs were transformed into *E. coli* BL21 codon plus cells and grown in LB supplemented with ampicillin, with overnight induction at 15°C, 0.15 mM IPTG. Purification was performed as described for EphB2. The mutations Tyr604Phe, Tyr610Phe, Pro607Gly, Phe620Asp, Ser680Trp, Gln684Trp, deletion of 599-606 (ΔJX1), deletion of 599-610 (ΔJX1+2), and deletion of 600-621 ($\Delta JX1_{all}$) in murine EphB2 were generated by site-directed mutagenesis using overlapping oligonucleotide primers containing the above indicated point mutations or deletions. All mutations were confirmed by DNA sequencing.

Western Blotting

GST-EphA4 proteins expressed in *E. coli* (BL21 codon plus), and EphB2 proteins transiently expressed in COS-1 cells, were harvested as previously described (Binns et al, 2000; Holland et al, 1997). Proteins were resolved using 12% denaturing polyacrylamide gel electrophoresis (PAGE), transferred onto a polyvinylidene difluoride membrane (Millipore), blotted with anti-pTyr (Upstate Biotechnology), anti-GST (Santa Cruz Laboratories), or anti-EphB2 antibodies (Holland et al., 1997), and visualized using enhanced chemiluminescence (ECL Plus; Amersham).

In vitro Kinase Reactions

In vitro kinase reactions using GST fusion EphA4 proteins bound to glutathione sepharose or immunoprecipitated EphB2 proteins transiently expressed in COS-1 cells were performed with 5 μg and 2 μg of acid-denatured enolase, respectively, and 5 μCi of [γ^{32}P]ATP at room temperature as previously described (Binns et al., 2000).

Spectrophotometric coupling assay

Kinetic analysis of the bacterial expressed EphA4 proteins was performed using a coupled *in vitro* spectrophotometric kinase assay where production of ADP is coupled to the oxidation of NADH through pyruvate kinase and lactic dehydrogenase (Barker et al., 1995; Binns et al, 2000). The 100-μl reaction volume contained 1 U lactic dehydrogenase, 1 U pyruvate kinase, 1 mM phosphoenolpyruvate, 0.2 mM NADH, and 0.5 mM ATP (in 20 mM $MgCl_2$, 0.1 mM DTT, 60 mM HEPES [pH 7.5], 20 μg/mL bovine serum albumin). Wild type and mutant EphA4 activity was measured by monitoring absorbance at 340 nm (Varian UV-Visible spectrophotometer) for 90 minutes at a fixed enzyme concentration (0.5 μM) and 1 mM S-1 synthetic peptide (GEEIYGEFD; amide at carboxy terminus) concentrations. For accuracy, protein concentrations were determined by UV spectrometry at 280 nm using molar extinction coefficients. (Andersson, 1998; Collaborative Computational Project, 1994).

Results and Discussions

Structure Determination

Since the expression of active EphB2 polypeptides in *E. coli* is toxic, efforts were focused on the catalytically repressed Tyr 604/610 Phe double mutant. For the purposes of discussion, these sites are referred to as Tyr/Phe 604 and Tyr/Phe 610. A cytoplasmic fragment (residues 595 to 906) of the murine EphB2 RTK consisting of the latter half of the juxtamembrane region and the entire catalytic domain was expressed as a GST fusion in *E. coli* and purified to homogeneity (see Methods). The predicted boundaries of the juxtamembrane region are residues 573-620, while those of the kinase and SAM domains are

residues 621-892 and residues 919-994, respectively. Protein crystals of two different space groups were grown and the EphB2 structure was determined using a combination of seleno-methionine multiwavelength anomalous dispersion (SeMet MAD) and molecular replacement (MR) methods (see Methods). The EphB2 crystal structure reported here corresponds to the juxtamembrane-catalytic domain fragment in complex with AMP-PNP (β, γ -imidoadenosine-5'-triphosphate). Overall, the EphB2 structure is well ordered except for the first seven and last six amino acid residues, kinase domain residues 651 to 653 connecting β-strands 2 and 3 of the N-terminal catalytic lobe, and residues 774 to 796 corresponding to the kinase activation segment within the C-terminal lobe. Only the adenine ring of AMP-PNP is ordered in experimental and model based electron density maps, and hence the sugar and phosphate groups have not been modeled. Data collection and refinement statistics are listed in Table 1 and a representative alignment of the EphB2 receptor and other protein kinase family members is provided in Figure 1.

Overall description of the autoinhibited structure

The structure of the catalytic domain of EphB2 conforms to that generally observed for protein kinases, consisting of two lobes, a smaller N-terminal lobe and larger C-terminal lobe (Figure 2a,b). Protein kinases are capable of a range of conformations owing to an inherent inter-lobe flexibility that allows for both open and closed conformations. However, the catalytically competent conformation is generally a closed structure in which the two catalytic lobes clamp together to form an interfacial nucleotide binding site and catalytic cleft. Surprisingly, the autoinhibited EphB2 catalytic domain adopts a closed conformation that resembles an 'active' state.

The N-terminal lobe of protein kinases consists minimally of a twisted 5-strand β-sheet (denoted β1 to β5 as first described for the cAMP dependent protein kinase (cAPK) and a single helix αC (Knighton et al., 1991). The N-terminal lobe functions to assist in the binding and coordination of ATP for the productive transfer of the γ-phosphate to a substrate oriented by the C-terminal lobe. In this regard, β-strands 1 and 2 and the glycine rich connecting segment (g-loop) form a flexible flap that interacts with the adenine base, ribose sugar and the non-hydrolyzable phosphate groups of ATP. Furthermore, an invariant salt bridge between a lysine side chain (sub-domain 2 in the protein kinase nomenclature of Hanks et al., 1988) in β-strand 3 and a glutamic acid side chain (sub-domain 3) in helix αC coordinates the β-phosphate of ATP. In the EphB2 crystal structure, all N-terminal lobe elements implicated in nucleotide binding are well ordered and adopt a prototypical protein kinase arrangement. However, distortions in helix αC and the g-loop arising from interactions with the juxtamembrane segment are evident.

The C-terminal lobe of protein kinases consists minimally of two β-strands (β7and β8) and a series of α-helices (αD to αI). Strands β7and β8 locate to the cleft region between the N- and C-terminal lobes where they contribute side chains that participate in catalysis and the binding of magnesium for the coordination of ATP phosphate groups. In the EphB2 crystal structure, all lower lobe residues implicated in catalysis and ATP coordination appear optimally oriented (Figure 3c). The activation segment, which is also located in the large catalytic lobe, is disordered as in several other protein kinase structures in which the activation segment is not phosphorylated (reviewed by Johnson et al., 1996). The remaining C-terminal

lobe elements, including α-helices αD to αI, are well ordered and adopt the prototypical protein kinase configuration. Terminating the catalytic domain structure is a short helix αJ.

The EphB2 juxtamembrane region preceding the catalytic domain is highly ordered and adopts an identical conformation in the four unique environments sampled in the two different crystal forms studied. From the amino-terminus, the conformation consists of an extended strand segment Ex1, a single turn 3/10 helix αA', and a four-turn helix αB'. These elements associate intimately with helix αC of the N-terminal catalytic lobe and also make limited interactions with the C-terminal lobe. As a consequence of the association of the juxtamembrane segment with the N-terminal kinase lobe, significant curvature is imposed on helix αC. This distortion couples directly to local distortions in other N-terminal lobe elements, most critically the g-loop and the invariant lysine-glutamate salt bridge. Together the N-terminal lobe distortions appear to impinge on catalytic function by adversely affecting the coordination of the sugar and phosphate groups of the bound nucleotide.

With limited contacts to the lower lobe of the catalytic domain, the juxtamembrane segment also sterically impedes the activation segment from adopting the productive conformation that typifies the active state of protein-serine/threonine and tyrosine kinases. Together, the effects on nucleotide coordination and the activation segment form the basis for autoinhibition of EphB2 by the juxtamembrane segment.

Depending on the splice variant of EphB2, there are 29-45 juxtamembrane residues between the start of strand Ex1 (Lys 602) and the plasma membrane (Connor and Pasquale, 1995). This relatively lengthy sequence makes it impossible to predict whether the autoinhibited structure observed here would be oriented in a specific fashion with respect to the inner surface of the membrane.

Detailed analysis of juxtamembrane structure

The juxtamembrane strand segment Ex1, corresponding to amino acid residues Lys 602 to Ile 605, extends along the cleft region between the N- and C-terminal lobes (Figure 2c,d). The phosphoregulatory residue Tyr/Phe 604 orients into a solvent-exposed hydrophobic pocket composed of the side chains of Met 748 and Tyr 750 of the C-terminal kinase lobe, Ile 681 and Phe 685 from helix αC and Pro 607 from the juxtamembrane helix αA'. This site has been termed 'switch region 1' since Tyr/Phe 604 appears well placed to influence the association of the juxtamembrane region with the catalytic domain. Further stabilizing the interaction of strand Ex1 with the lower catalytic lobe are hydrogen bonds between the amide group of Tyr/Phe 604 and the carbonyl group of Met 748 and between the side chain of Gln 684 and the backbone amide and carbonyl groups of Ile 605.

Helix αA' is composed of a single rigid turn initiated by an Asp606Pro607 sequence and terminated by Thr 609. This helix appears stabilized by the conformational rigidity of Pro 607 and the capping interactions involving the side chains of Asp 606 and Thr 609 with the free backbone amino group and carbonyl groups of Phe 608 and Asp 606. A short linker and then a three-turn helix αB', initiated by Asp 612Pro613 and extending to Phe 620, follow helix αA'. Helix αB' is also initiated by an Asp Pro sequence (residues 612 and 613) and Asp 612 makes similar capping interactions with the backbone amino and side chain of Asn 614. Helices αA' and αB' form an interface with the N-terminal lobe of the kinase

that centers on helix αC. Hydrophobic side chains projecting from αA' and αB' include Pro 607, Phe 608, Pro 613, Val 617, Phe620 and Ala 621. These residues associate intimately with Arg 673, Leu 676, and Ile 681 from helix αC and Leu 693 and Val 696 from β-strand 4. In addition, a hydrogen bond interaction (2.9Å) is observed between Asn 614 and Arg 672 (Figure 2c), and the small side chains at positions 616 (Ala), 677 (Ser) and 680 (Ser) facilitate the close packing of helices αA', αB' and αC.

Opposite to, but contiguous with, the site of association with helix αC, strand Ex1 and helices αA' and αB' form an interface composed primarily of hydrophobic interactions. The side chain of the phosphoregulatory residue Tyr/Phe 610 projects onto the surface of this site and appears well positioned to exert an influence on the local juxtamembrane structure. This interface, termed 'switch region 2', is composed of the side chains of Ile 605 from strand Ex1 and the side chains of Ala 616 and Phe 620 from helix αB'.

Effect of the juxtamembrane engagement on the N-terminal lobe structure

Comparison of the EphB2 crystal structure with that of the 'active' triply phosphorylated insulin receptor tyrosine kinase (active IRK (Hubbard, 1997)) indicates the mechanism by which the juxtamembrane region of EphB2 inhibits the catalytic domain. Superposition of C-terminal kinase lobe elements places the majority of N-terminal lobe elements into close correspondence (Figure 3a-d). A distinguishing feature of the EphB2 structure is a 14° kink midway along helix αC centered at Glu 678. This kink, which coincides with the site of association with the juxtamembrane elements Ex1, αA' and αB', displaces the forward facing N-terminus of helix αC 6.8 Å upward and outward from the equivalent position observed in IRK (Figure 3a,c). Stabilizing this kink internally are side chain/main chain interactions involving Ser 677 and Ser 680.

The kink in helix αC places its forward projecting terminus in close proximity to β-strands 3, 4, and 5, forming a tighter interface than that observed in active IRK (Figure 3b). Residues participating in this interface include Arg 672, Phe 675, and Leu 676 from helix αC, Tyr 667 from the β3 / αC linker and Leu 663, Val 696, Thr 698, Val 703, and Ile 705 from the β-strands. Interestingly, tyrosine 667, which is centrally positioned within this interface and is highly conserved amongst the Eph receptor family members, has been identified as an *in vivo* site of phosphorylation (Kalo and Pasquale, 1999), suggesting a possible phosphoregulatory role.

The close association of helix αC with β-strands 3, 4 and 5 is achieved with a local alteration to the twist of the forward projecting termini of β-strands 1, 2 and 3 that leaves the bulk of the N-terminal sheet structure unperturbed. The g-loop side chain Phe 640 plays a role in coupling the β-strand movements to that of helix αC through a direct interaction with Phe 675. The altered twist of the β1, β2 and β3-strand termini displace main chain atoms at the end of the g-loop (Glu 639 and Phe 640) by approximately 3.3 Å. In addition, together with the kink in helix αC, the altered twist of the β-strands displaces the invariant glutamate and lysine side chains by 2.4 and 2.1 Å, respectively, relative to their positions in active IRK (Figure 3c). As a consequence, the ability of the catalytic domain to coordinate the sugar and phosphate groups of bound nucleotide is compromised (Figure 3a-c). Since the domain closure

and the bulk of the N-terminal β-sheet structure is not perturbed, the adenine binding pocket is well formed and indeed the adenine base of bound AMP-PNP is ordered and orients in a manner similar to that in the crystal structure of active IRK.

Steric influence of the juxtamembrane region on the activation segment

While the majority of interactions between the juxtamembrane segment and the catalytic domain are directed towards the N-terminal lobe, strand Ex1 forms a limited set of interactions with the C-terminal lobe that may serve a regulatory role. Superposition of EphB2 with active IRK illustrates how the side chain of the phosphoregulatory residue Tyr/Phe 604 impedes the activation segment from adopting a productive conformation (Figure 3d). In autoinhibited EphB2, the side chain of Tyr 750 adopts an alternate conformation from that of the corresponding residue Phe 1128 in active IRK. This avoids a steric clash with the side chain of Tyr/Phe604. The alternate conformation of Tyr 750, in turn, impedes the activation segment from adopting a path observed in active IRK due to a steric clash with Ser 776 (Thr 1154 in IRK). Interestingly, the side chain conformation of Tyr 750 in EphB2, Tyr 382 in Src and Hck, and Phe 1128 in IRK all correlate with their activation segments adopting non-productive conformations. This may be indicative of a more general function in protein kinases for position 750 in regulating the conformation of the activation segment.

The phosphoregulatory switch

The ability to oscillate between catalytically active and repressed states in a regulated manner is the key to the function of protein kinases as versatile molecular switches. In EphB2, EphA4, and most likely Eph RTKs in general, the switch to an active state is coordinated by phosphorylation at highly conserved sites within both the juxtamembrane region and the catalytic domain. The mechanism by which phosphorylation at sites within the activation segment stimulate protein kinases is relatively well understood (reviewed by Johnson *et al.*, 1996) and by inference, phosphorylation of EphB2 at Tyr 788 likely promotes the ordering of the activation segment to a catalytically competent conformation.

In contrast, phosphorylation at Tyr/Phe 604 and 610 may serve to destabilize the juxtamembrane structure and cause it to dissociate from the catalytic domain. This would allow for a return of the N-terminal lobe to an undistorted active conformation.

The EphB2 crystal structure helps to explain how phosphorylation at each of the two phosphoregulatory sites could destabilize the juxtamembrane structure and cause its release from the catalytic domain. The environment around each of the two switch regions is hydrophobic, but solvent exposed, and thus could accommodate either tyrosine or phenylalanine at positions 604 and 610 with little or no reorganization of the juxtamembrane structure. However, substitution with phosphotyrosine appears less tolerable due to steric and electrostatic clashes involving the bulky anionic phosphate group. In 'switch region 1', the phosphorylation of Tyr/Phe 604 would place a phosphate group within van der Waals contact of Asp 606, Pro 607 and Ile 681. Furthermore, the side chain of Asp 606 dominates the electrostatic environment around Tyr/Phe 604 such that the introduction of a phosphate group would generate repulsive electrostatic forces (Figure 4). The electrostatic environment around 'switch region 2' is also dominated by negatively charged amino acids, namely Asp 606, Glu 611, Asp 612, Glu 615, and

Glu 619. Thus, phosphorylation of Tyr 610 would also generate repulsive electrostatic forces, which are likely essential for the expulsion of this residue from its binding pocket since a phosphate group could be accommodated sterically.

Three other highly conserved tyrosine residues have been identified as *in vivo* phosphorylation sites in EphB2 and EphB5, namely tyrosines 667, 744 and 750 (Figure 3c). Although their roles in regulating Eph receptor kinase activity have not been probed by mutagenesis, all three sites appear well positioned to influence the stability of the autoinhibited structure and hence Eph receptor activity (Figure 3). For example, phosphorylation of Tyr 667 could promote a catalytically competent state by destabilizing the tight association of helix αC with β-strands 3, 4 and 5 observed in the autoinhibited state. In addition, phosphorylation of Tyr 744 and Tyr 750, which line the cleft region through which the juxtamembrane strand Ex1 navigates, could amplify the effect of phosphorylation at Tyr 604.

Function of the EphA4 juxtamembrane segment probed by mutagenesis

Previously, a cytoplasmic fragment of the EphA4 receptor tyrosine kinase, consisting of the juxtamembrane segment, the catalytic domain and the SAM domain, has been shown to require autophosphorylation for maximal activation (Binns et al., 2000). The importance of autophosphorylation was revealed by a lag period at the start of *in vitro* kinase reactions employing the dephosphorylated form of the EphA4 enzyme. This lag period was greatly reduced by pre-incubation of the EphA4 fragment with ATP or by deletion of the entire juxtamembrane segment. In contrast, mutation to phenylalanine of either Tyr 604 or Tyr 610 reduced the specific activity of the enzyme, while mutation of both sites in tandem drastically impaired catalytic function (<10% relative to WT). These results are consistent with the mechanism of autoinhibition suggested by the EphB2 crystal structure.

In order to test the crystallographic findings and to probe the regulation of Eph receptor catalytic activity in more detail, additional site-directed mutations were generated in the full-length murine EphB2 receptor expressed in COS-1 cells and in a murine EphA4 receptor fragment expressed in bacteria, corresponding in content to the EphB2 construct used for the structure determination. For the sake of discussion, the murine EphB2 numbering scheme has been employed for all mutants and the corresponding EphA4 residue numbers are listed in parentheses. Each mutation was generated in the catalytically repressed Tyr 604/610 Phe double mutant background and was tested for its ability to restore catalytic function. The mutations include a small N-terminal deletion of residues 595 to 606 (ΔJX1) encompassing strand Ex1 and the first phosphoregulatory site, an intermediate N-terminal deletion of residues 599 to 610 (ΔJX1+2) that encompasses strand Ex1, the first phosphoregulatory site, helix αA' and the second phosphoregulatory site, and a full juxtamembrane segment deletion of residues 599 to 621 (ΔJX_{all}). In addition, six separate point mutations were generated in both the juxtamembrane region and the kinase domain (Pro607Gly, Phe608Asp, Phe620Asp, Tyr604/610Glu, Ser680Trp, Gln684Trp) that were predicted to destabilize the interaction of the kinase domain with the juxtamembrane segment. Lastly, the ΔJX1+2 mutation was combined with the Phe620Asp mutation (ΔJX1+2 plus Phe620Asp) and the Ser680Trp mutation was combined with the Gln684Trp mutation (Ser680Trp/Gln684Trp). The Tyr604/610Phe double mutant and the wild type proteins were analyzed concomitantly as reference points for the fully repressed

(0%) and active (100%) states, respectively. The activities of the EphA4 proteins expressed in bacteria were tested for their ability to induce protein tyrosine phosphorylation in vivo (Figure 5a), and to autophosphorylate and to phosphorylate enolase in vitro (Figure 5b). EphA4 proteins were also tested for their ability to phosphorylate a peptide substrate using a continuous spectophotometric assay (Figure 5c). Lastly, full-length EphB2 proteins expressed in COS-1 cells were tested for their ability to autophosphorylate *in vivo* and to autophosphorylate and phosphorylate enolase *in vitro* (Figure 5d).

The two partial N-terminal juxtamembrane deletions when introduced into the EphA4 construct significantly increased kinase activity in all four assays, restoring catalytic function as measured by the spectrophotometric assay to 136% and 216% of wild-type activity in the case of ΔJX1 and the ΔJX1 +2 deletions, respectively. A similar effect was observed for the ΔJX1 +2 deletion introduced into full-length EphB2.

Mutation of Phe 608 in EphA4, which locates to helix αA', gave very weak restoration of catalytic function. This result is consistent with the variability of position 608 amongst the Eph receptor family members (42% identity). In contrast, mutation in both EphA4 and EphB2 constructs of the highly conserved Pro 607 (95% identity), which initiates helix αA', to Gly greatly enhanced catalytic function in all four assays, quantitated at 122% of wild-type activity by the spectrophotometric assay. This result is consistent with a role for Pro607, suggested by the crystal structure, in stabilizing helix αA' by imposing conformational rigidity, or in promoting the association of juxtamembrane and N-terminal kinase lobe elements through hydrophobic interactions. Similarly, mutation of the highly conserved Phe 620 (95% identity) at the terminus of helix αB' to Asp also restored catalytic function in the four assays tested. Phe 620 is notable because it contributes to the hydrophobic pocket into which the phosphoregulatory residue Tyr/Phe 610 binds; its substitution with Asp is predicted to disrupt the hydrophobic interaction with Tyr/Phe 610, and to clash electrostatically with the surrounding negatively charged groups in a manner mimicking phosphorylation of Tyr/Phe 610.

The introduction of point mutations into the kinase domain at the interface with the juxtamembrane region also restored catalytic function. Mutation of Ser680 (82% identity) to Trp in both EphA4 and EphB2 constructs gave modest restoration with the phosphorylation of peptide substrate being restored to 41% of wild-type activity. Mutation of the absolutely conserved Gln684 (100% identity) to Trp in EphB2 resulted in a greater increase in kinase activity, as did the double mutation Ser 680Trp/Gln684Trp. Both mutations map to helix αC and are predicted to sterically perturb the association of the juxtamembrane region with the N-terminal catalytic lobe.

Robust restoration of activity was also observed for the EphA4 and EphB2 mutants ΔJX_{all}, Tyr604/610Glu, and ΔJX1+2 plus Phe620Asp, although the relative restoration as measured by the various assays differed to a small degree. The restoration of activity by the ΔJX_{all} mutant confirms that the juxtamembrane segment is not absolutely required for kinase function, the restoration by the Tyr604/610Glu mutation suggests that the addition of negative charges at positions 604 and 610 is an important component of juxatmembrane destabilization and the relief of autoinhibition. Lastly, the finding that none of the EphB2 mutants are as active as the wild-type enzyme may indicate that these mutants have

perturbed some aspect of the oligomerization event that is needed for maximal activation of the full-length receptor.

Overall, the mutagenesis results support a model for the regulation of receptor catalytic function by the juxtamembrane segment, shown in Figure 6. Strand Ex1 and helix αA' of the juxtamembrane segment contribute to the inhibitory effect on the catalytic domain, and the release of these elements from their association with the catalytic domain is a requirement for catalytic activation. Physiologically, this would be accomplished by phosphorylation at the Tyr 604 and 610 regulatory sites and potentially at additional sites. The strong conservation of residues involved in the inhibitory interaction suggests that this regulatory mechanism is conserved for all Eph receptor family members.

Comparison of Autoinhibitory Mechanisms of EphB2 and TGFβR1 Receptor Kinase

Analysis of the TGFβR1 serine/threonine kinase has revealed a role for the juxtamembrane Gly/Ser/Thr-rich motif ("GS segment") in regulating catalytic activity. As with Eph receptor tyrosine kinases, TGFβR1 kinases require phosphorylation at sites within the juxtamembrane segment for subsequent phosphorylation of target Smad proteins (Macias-Silva et al, 1996). The regulatory mechanism revealed by the X-ray crystal structure of a cytoplasmic fragment of TGFβR1 in complex with FKBP12 (Huse et al, 1999) shows some parallels to EphB2. In both structures, the intramolecular engagement of the juxtamembrane segment induces conformational distortions in the catalytic domain that impinge on kinase function. In addition, the induced distortions impact on the relative positioning and/or conformation of helix αC. Beyond these similarities, however, the inhibitory mechanisms, including the mode of juxtamembrane association with the catalytic domain and the resulting basis for inhibition, diverge. Perhaps the most significant difference relates to the potential involvement of FKBP12 in stabilizing the inhibited structure of TGFβR1, whereas EphB2 achieves an autoinhibited state independently. Nonetheless, the data for EphB2 indicate that receptor tyrosine kinases and receptor serine/threonine kinases have in some cases converged on a related regulatory mechanism in which the juxtamembrane region inhibits the kinase domain in the inactive state, and is potentially liberated to interact with downstream targets upon autophosphorylation.

Discussion

Why does EphB2 employ a rather complex mechanism of autoregulation, involving the non-catalytic juxtamembrane region? One possible benefit may be to block any potential signaling activity intrinsic to the juxtamembrane sequence. In particular, phosphorylation of tyrosines 604 and 610 in EphB2 creates docking sites for SH2 domain proteins. Sequestering these tyrosines decreases their chance of becoming adventitiously phosphorylated and thereby inappropriately transmitting a signal through the recruitment of downstream targets. The coordination of kinase activation with the release of binding sites for targets is reminiscent of Src family cytoplasmic tyrosine kinase, in which the SH2 and SH3 domains engage internal ligands in a fashion that both inhibits the activity of the kinase domain and hinders interactions of the SH2 and SH3 domains with other binding partners (Sicheri et al., 1997; Xu et al., 1997).

The involvement of the juxtamembrane sequence in autoregulation of EphB2 activity may also set a phosphorylation threshold that must be exceeded to induce receptor activation. Full stimulation of Eph

receptors apparently requires autophosphorylation at multiple sites within both the activation segment and juxtamembrane region. The use of at least two distinct phosphoregulatory steps may preclude inappropriate Eph receptor activation resulting from basal levels of kinase activity. Since Eph receptors have powerful biological activities during embryogenesis and postnatally, their aberrant activation would be expected to have severe phenotypic consequences, which could be avoided by requiring multi-site phosphorylation of the receptor.

Are the Eph receptors unique among RTKs in employing cytoplasmic elements outside the catalytic domain to regulate kinase activity? A variety of data obtained for the platelet-derived growth factor β receptor (PDGFR), the closely related colony stimulating factor-1 receptor (c-Fms), stem cell factor receptor (Kit), and the Flt3 receptor raise the possibility that this may in fact be a more widespread phenomenon. Biochemical analysis and mutagenesis of the PDGFR-β has suggested that autophosphorylation of juxtamembrane tyrosines 579 and 581 is required for stimulation of receptor kinase activity by PDGF, potentially by allowing subsequent phosphorylation of tyrosine 857 in the activation segment (Baxter et al., 1998). Conversion of these juxtamembrane tyrosines to phenylalanine inhibits receptor activation, while their phosphorylation creates a binding site for the Src SH2 domain, resulting in Src recruitment to the receptor. Thus, autophosphorylation within the juxtamembrane region of the PDGFR-β may couple receptor activation to the exposure of SH2 domain-binding sites, as appears to be the case for Eph receptors. Consistent with the notion that the juxtamembrane region of the PDGFR-β exerts an inhibitory influence on kinase activity, substitution of a valine residue, just N-terminal to the regulatory tyrosines, results in constitutive receptor activation *in vitro* and *in vivo* (Irusta and DiMaio, 1998). In addition to the PDGFR-β, the juxtamembrane regions of c-Fms (Myles et al., 1994), Kit, and Flt3 receptors have been implicated in regulation of tyrosine kinase activity. Oncogenic variants of Kit identified in human and murine mast cell leukemias carry either amino acid substitutions or deletions in the juxtamembrane region, which result in constitutive activation of the kinase domain (Tsujimura et al., 1996)(see Figure 1). Remarkably a majority of human gastrointestinal stromal tumors (GIST) have activating Kit mutations that introduce substitutions or deletions into a short segment of the juxtamembrane region, and are strongly implicated in the etiology of these tumors (Hirota et al, 1998; Nakahara et al; 1998; Anderson, 1998). Furthermore, approximately 20% of acute myeloid leukemias have internal tandem duplications of Flt3 that create in-frame insertions of variable length in the juxtamembrane region, leading to ligand-independent kinase activity and oncogenic acitvation (Nakao et al, 1996; Yokota et al, 1997; Hayakawa et al, 2000). Thus, Kit and Flt3 juxtamembrane regions may repress kinase activity, and juxtamembrane mutations that relieve this inhibition can result in human cancers.

A similar situation may pertain for the insulin receptor, which upon activation becomes autophosphorylated within the juxtamembrane region and consequently binds targets such as IRS-1 and ShcA, which possess PTB domains. Kinetic analysis of wild type and mutant insulin receptors has suggested that the insulin receptor juxtamembrane region acts as an intrasteric inhibitor to block the kinase domain active site, in a fashion that is relieved by autophosphorylation of juxtamembrane tyrosines (Cann et al., 2000).

Many RTKs have C-terminal tails that upon activation become phosphorylated at SH2/PTB domain-binding sites. Structural analysis of the Tie2/Tek receptor cytoplasmic region has indicated that in the inactive state the tail interacts with the kinase domain in a way that partially occludes the C-terminal tyrosines and the peptide binding site (Shewchuk et al., 2000). This raises the possibility that autophosphorylation of the Tie2 tail causes a conformational change that exposes both C-terminal phosphotyrosine sites as well as the substrate binding site of the kinase domain.

Thus the juxtamembrane and C-terminal segments of RTKs may play a pivotal role in regulating the kinase domain, and in coordinating enzymatic activation with the exposure of motifs that bind cytoplasmic targets.

In addition to revealing an unexpected level of complexity in the regulation of RTKs, these observations have interesting implications for the design of RTK inhibitors. The structure of the Abl kinase bound to the inhibitor STI-571 suggests that this compound binds selectively to the inactive form of the kinase (Schindler et al., 2000). The unusual structure of autoinhibited EphB2 suggests the possibility of isolating inhibitors that bind specifically to the inactive conformation of the kinase. Indeed, if this mode of intrasteric regulation is a more common feature of RTKs, this might be a general strategy for the identification of selective RTK inhibitors.

The structure of EphB2 reveals an entirely novel mechanism for RTK autoregulation.

All publications mentioned in the above specification are herein incorporated by reference. Various modifications and variations of the described methods and system of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with specific preferred embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in chemistry, biology or related fields are intended to be within the scope of the following claims.

Table 1 Data collection, structure determination and refinement statistics

	SeMet MAD Analysis			Native
	λ_1 = 0.9790 Å	λ_2 = 0.9788 Å	λ_3 = 0.9770 Å	(AMP-PNP)
Spacegroup	$P2_1$	$P2_1$	$P2_1$	P1
Resolution (Å)	2.3	2.3	2.3	1.9
Reflections total/unique	185034/52252	188170/52750	186452/52855	80035/43865
Completeness (%)*	97.5 (91.2)	97.6 (91.7)	97.6 (90.8)	90.3 (55.9)
Rsym (%)*†	7.4 (26.2)	7.5 (27.9)	8.5 (38.7)	3.3 (14.6)
<I/σ>*	15.6 (4.0)	16.1 (3.9)	14.9 (3.1)	20.9 (4.1)
Phasing Power‡ (ISO/ANO)	0/2.59	2.71/4.11	2.08/3.40	-

Refinement (AMP-PNP complex)

Resolution Range (Å)	30-1.9	Average B value (Å^2)	24.9
Reflections		Rmsd for B values (Å^2)	1.42
all data	42903	Rmsd for bonds (Å)	0.007
|F|>2σ	39931	Rmsd for angles (°)	1.09
R_{factor} / R_{free} (%)**			
all data	24.1/27.7	Number of non-hydrogen protein atoms	4311
|F|>2σ	23.2/26.9		
		Number of non-hydrogen nucleotide atoms	20
		Number of water molecules	263

*Numbers given in parentheses refer to data for the highest resolution shell. †Rsym = 100 × $\sum$|I-<I>|/$\sum$<I>, where I is the observed intensity and <I> is the average intensity from multiple observations of symmetry-related reflections. ‡Phasing power for isomorphous and anomalous acentric reflections, where P_{power} = < [| F_h(calc) / phase-integrated lack of closure] >.
**Free R-value was calculated with 8.7% of the data.

Table 2. Intermolecular contacts of the Juxtamembrane Region and Kinase Domain of an Eph Receptor

No. of Atomic Interaction	Juxtamembrane Region Atomic Contact	Kinase Domain/Juxta-membrane Region Atomic Contact	Distance Between Atomic Contacts	Atomic Interaction Property
1	Phe/Tyr 604 CB	Met 748 CE	4.58	hydrophobic
2	Phe/Tyr 604 N	Met 748 O	2.83	H-bond
3	Phe/Tyr 604 CD2	Tyr 750 CD1	3.78	Hydrophobic
4	Phe/Tyr 604 CE2	Tyr 750 CE1	4.12	Hydrophobic
5	Phe/Tyr 604 CD1	Phe 685 CE2	4.06	Hydrophobic
6	Ile 605 N	Gln 684 OE1	2.83	H-bond
7	Ile 605 O	Gln 684 NE2	3.00	H-bond
8	Phe/Tyr 604 CE1	Gln 684 CD	4.11	van der Waal
9	Pro 607 CD	Ile 681 CG1	3.85	Hydrophobic
10	Pro 607 CB	Ser 680 OG	3.16	van der Waal
11	Phe 608 CZ	Asp 674 OD1	3.27	van der Waal
12	Phe 608 CZ	Ser 677 CB	4.35	van der Waal
13	Phe 608 CE2	Arg 673 CG	3.79	Hydrophobic
14	Pro 613 CB	Arg 673 CD	3.60	Hydrophobic
15	Asn 614 OD1	Arg 672 NH1	2.87	H-bond
16	Val 617 CG2	Leu 676 CD1	4.69	Hydrophobic
17	Val 617 CG2	Ser 680 CB	4.15	Hydrophobic
18	Val 617 CG2	Leu 676 CB	4.10	Hydrophobic
19	Ala 621 CB	Leu 693 CD2	3.98	Hydrophobic
20	Phe 620 CD1	Gln 684 CG	3.60	Hydrophobic
21	Phe 620 CE1	Gln 684 CD	3.77	Hydrophobic
22	Phe 620 CB	Gln 683 O	4.15	van der Waal
23	Phe 620 O	Gln 683 O	3.41	H-bond
24	Ala 616 CA	Ser 680 CB	3.8	Hydrophobic
25	Tyr/Phe 604 CE2	Asp 606 CB	4.26	Hydrophobic
26	Pro 607 CD	Asp 606 OD1	3.28	van der Waal
27	Asp 606 O	Thr 609 OG1	2.72	Hydrogen bond
28	Asp 606 O	Thr 609 N	2.90	Hydrogen bond
29	Asp 606 CB	Thr 609 CG2	3.56	Hydrophobic
30	Phe 604 CZ	Pro 607 CD	3.90	Hydrophobic
31	Pro 607 O	Phe 610 N	3.08	Hydrogen bond
32	Phe 608 CD2	Pro 613 CG	4.43	Hydrophobic
33	Phe 610 CE1	Ile 605 CG2	3.48	Hydrophobic
34	Phe 610 CZ	Phe 620 CE1	3.91	Hydrophobic
35	Phe 610 CE1	Ala 616 CB	3.91	Hydrophobic
36	Phe 610 CD2	Glu 615 CG	3.74	Hydrophobic
37	Asp 612 O	Glu 615 N	2.73	Hydrogen bond
38	Phe 608 N	Asp 606 OD1	2.83	Hydrogen Bond
39	Asp 612 OD1	Asn 614 ND2	3.09	Hydrogen bond
40	Asp 612 OD1	Asn 614 N	3.11	Hydrogen bond
41	Asn 614 O	Arg 618 N	3.16	Hydrogen bond
42	Pro 613 O	Val 617 N	3.59	Weak hydrogen bond, van der Waal
43	Glu 615 O	Glu 619 N	3.06	Hydrogen Bond
44	Glu 615 OE1	Glu 619 OE1	2.64	Hydrogen Bond
45	Phe 620N	Ala 616 O	2.96	Hydorgen Bond
46	Glu 619 OE2	Phe 620 CZ	4.03	Van der waals
47	Ala 621 N	Val 617 O	2.91	Hydrogen Bond

48	Ala 621 O	Val 617 O	3.25	Hydrogen Bond
49	Ala 621 CB	Val 617 CG1	4.16	Hydrophobic

Table 3

```
REMARK coordinates from minimization and B-factor refinement
□
REMARK refinement resolution: 30 - 1.9 A
REMARK starting r= 0.2330 free_r= 0.2672
REMARK final    r= 0.2316 free_r= 0.2691
REMARK rmsd bonds= 0.007125  rmsd angles=  1.07641
REMARK B rmsd for bonded mainchain atoms=  1.398  target= 1.5
REMARK B rmsd for bonded sidechain atoms=  1.963  target= 2
REMARK B rmsd for angle mainchain atoms=  2.128  target= 2
REMARK B rmsd for angle sidechain atoms=  2.727  target= 2.5
REMARK target= mlf  final wa= 1.79025
REMARK final rweight=  0.1000 (with wa= 1.79025)
REMARK md-method= torsion  annealing schedule= slowcool
REMARK starting temperature= 3000  total md steps= 30 * 6
REMARK cycles= 2 coordinate steps= 20 B-factor steps= 10
REMARK sg= P1 a= 47.052 b= 57.616 c= 67.742 alpha= 112.949 beta= 103.173 gamma=
91.577
REMARK topology file 1  : CNS_TOPPAR:protein.top
REMARK topology file 2  : CNS_TOPPAR:dna-rna.top
REMARK topology file 3  : CNS_TOPPAR:water.top
REMARK topology file 4  : CNS_TOPPAR:ion.top
REMARK topology file 5  : adenine.top
REMARK parameter file 1  : CNS_TOPPAR:protein_rep.param
REMARK parameter file 2  : CNS_TOPPAR:dna-rna_rep.param
REMARK parameter file 3  : CNS_TOPPAR:water_rep.param
REMARK parameter file 4  : CNS_TOPPAR:ion.param
REMARK parameter file 5  : adenine.par
REMARK molecular structure file: gen_ab.mtf
REMARK input coordinates: ref7b.pdb
REMARK reflection file= ../cycle1/amp.cv
REMARK ncs= none
REMARK B-correction resolution: 6.0 - 1.9
REMARK B-factor correction applied to coordinate array B:    0.210
REMARK bulk solvent: density level= 0.37437 e/A^3, B-factor= 62.0599 A^2
REMARK reflections with |Fobs|/sigma_F < 2 rejected
REMARK reflections with |Fobs| > 10000 * rms(Fobs) rejected
REMARK theoretical total number of refl. in resol. range:     49847 ( 100.0 % )
REMARK number of unobserved reflections (no entry or |F|=0):   6944 (  13.9 % )
REMARK number of reflections rejected:                         2972 (   6.0 % )
REMARK total number of reflections used:                      39931 (  80.1 % )
REMARK number of reflections in working set:                  35881 (  72.0 % )
REMARK number of reflections in test set:                      4050 (   8.1 % )
CRYST1   47.052   57.616   67.742 112.95 103.17  91.58 P 1
REMARK FILENAME="ref7c.pdb"
REMARK DATE:18-Jan-01  11:50:14       created by user: groot
REMARK VERSION:1.0
ATOM      1  CB  LYS A 602      -9.305  -0.312 -16.924  1.00 36.55      A
ATOM      2  CG  LYS A 602      -9.592  -1.380 -17.964  1.00 40.76      A
ATOM      3  CD  LYS A 602      -9.801  -2.735 -17.332  1.00 43.15      A
ATOM      4  CE  LYS A 602     -10.202  -3.766 -18.379  1.00 46.04      A
ATOM      5  NZ  LYS A 602     -10.292  -5.135 -17.793  1.00 47.27      A
ATOM      6  C   LYS A 602      -9.501   2.125 -16.413  1.00 30.61      A
ATOM      7  O   LYS A 602      -8.689   3.021 -16.178  1.00 31.27      A
ATOM      8  N   LYS A 602      -7.962   1.290 -18.245  1.00 34.40      A
ATOM      9  CA  LYS A 602      -9.247   1.097 -17.512  1.00 33.41      A
ATOM     10  N   ILE A 603     -10.653   1.995 -15.761  1.00 26.03      A
ATOM     11  CA  ILE A 603     -11.041   2.890 -14.680  1.00 21.35      A
ATOM     12  CB  ILE A 603     -12.110   3.916 -15.127  1.00 23.23      A
ATOM     13  CG2 ILE A 603     -13.424   3.183 -15.474  1.00 23.72      A
ATOM     14  CG1 ILE A 603     -12.383   4.899 -13.988  1.00 22.54      A
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ATOM	15	CD1	ILE	A	603	-13.398	5.974	-14.316	1.00	27.41	A
ATOM	16	C	ILE	A	603	-11.648	2.050	-13.553	1.00	17.90	A
ATOM	17	O	ILE	A	603	-12.280	1.022	-13.815	1.00	16.74	A
ATOM	18	N	PHE	A	604	-11.460	2.501	-12.313	1.00	12.95	A
ATOM	19	CA	PHE	A	604	-11.981	1.815	-11.122	1.00	14.58	A
ATOM	20	CB	PHE	A	604	-11.309	2.347	-9.848	1.00	13.58	A
ATOM	21	CG	PHE	A	604	-11.978	1.890	-8.569	1.00	10.12	A
ATOM	22	CD1	PHE	A	604	-11.890	0.565	-8.165	1.00	12.14	A
ATOM	23	CD2	PHE	A	604	-12.683	2.785	-7.770	1.00	12.13	A
ATOM	24	CE1	PHE	A	604	-12.493	0.132	-6.972	1.00	12.82	A
ATOM	25	CE2	PHE	A	604	-13.293	2.368	-6.574	1.00	13.41	A
ATOM	26	CZ	PHE	A	604	-13.194	1.036	-6.176	1.00	11.79	A
ATOM	27	C	PHE	A	604	-13.488	2.027	-10.968	1.00	14.34	A
ATOM	28	O	PHE	A	604	-13.972	3.155	-11.068	1.00	14.17	A
ATOM	29	N	ILE	A	605	-14.205	0.946	-10.671	1.00	14.05	A
ATOM	30	CA	ILE	A	605	-15.658	0.985	-10.471	1.00	15.51	A
ATOM	31	CB	ILE	A	605	-16.376	-0.024	-11.404	1.00	14.91	A
ATOM	32	CG2	ILE	A	605	-17.892	0.062	-11.203	1.00	17.40	A
ATOM	33	CG1	ILE	A	605	-16.034	0.269	-12.868	1.00	16.70	A
ATOM	34	CD1	ILE	A	605	-16.412	1.664	-13.326	1.00	20.67	A
ATOM	35	C	ILE	A	605	-15.976	0.616	-9.010	1.00	15.81	A
ATOM	36	O	ILE	A	605	-15.679	-0.491	-8.569	1.00	17.18	A
ATOM	37	N	ASP	A	606	-16.547	1.548	-8.253	1.00	16.32	A
ATOM	38	CA	ASP	A	606	-16.902	1.291	-6.855	1.00	17.50	A
ATOM	39	CB	ASP	A	606	-17.542	2.550	-6.253	1.00	18.47	A
ATOM	40	CG	ASP	A	606	-17.884	2.403	-4.775	1.00	19.43	A
ATOM	41	OD1	ASP	A	606	-17.942	1.262	-4.272	1.00	20.86	A
ATOM	42	OD2	ASP	A	606	-18.114	3.440	-4.115	1.00	20.82	A
ATOM	43	C	ASP	A	606	-17.899	0.128	-6.844	1.00	18.22	A
ATOM	44	O	ASP	A	606	-19.001	0.249	-7.371	1.00	17.14	A
ATOM	45	N	PRO	A	607	-17.517	-1.014	-6.247	1.00	17.74	A
ATOM	46	CD	PRO	A	607	-16.268	-1.278	-5.509	1.00	17.77	A
ATOM	47	CA	PRO	A	607	-18.427	-2.164	-6.209	1.00	18.01	A
ATOM	48	CB	PRO	A	607	-17.621	-3.247	-5.470	1.00	17.22	A
ATOM	49	CG	PRO	A	607	-16.645	-2.465	-4.633	1.00	18.76	A
ATOM	50	C	PRO	A	607	-19.753	-1.836	-5.536	1.00	16.89	A
ATOM	51	O	PRO	A	607	-20.780	-2.404	-5.878	1.00	17.69	A
ATOM	52	N	PHE	A	608	-19.744	-0.897	-4.602	1.00	17.34	A
ATOM	53	CA	PHE	A	608	-20.989	-0.557	-3.946	1.00	19.12	A
ATOM	54	CB	PHE	A	608	-20.738	0.133	-2.613	1.00	18.91	A
ATOM	55	CG	PHE	A	608	-20.319	-0.799	-1.511	1.00	18.72	A
ATOM	56	CD1	PHE	A	608	-20.047	-0.291	-0.251	1.00	18.84	A
ATOM	57	CD2	PHE	A	608	-20.171	-2.166	-1.729	1.00	18.90	A
ATOM	58	CE1	PHE	A	608	-19.632	-1.114	0.776	1.00	20.59	A
ATOM	59	CE2	PHE	A	608	-19.750	-3.011	-0.693	1.00	22.14	A
ATOM	60	CZ	PHE	A	608	-19.482	-2.478	0.559	1.00	19.82	A
ATOM	61	C	PHE	A	608	-21.928	0.292	-4.795	1.00	18.67	A
ATOM	62	O	PHE	A	608	-22.993	0.678	-4.319	1.00	18.02	A
ATOM	63	N	THR	A	609	-21.546	0.609	-6.031	1.00	18.97	A
ATOM	64	CA	THR	A	609	-22.463	1.373	-6.868	1.00	19.12	A
ATOM	65	CB	THR	A	609	-21.748	2.284	-7.911	1.00	17.33	A
ATOM	66	OG1	THR	A	609	-20.955	1.487	-8.799	1.00	17.70	A
ATOM	67	CG2	THR	A	609	-20.886	3.309	-7.216	1.00	18.57	A
ATOM	68	C	THR	A	609	-23.313	0.342	-7.606	1.00	19.52	A
ATOM	69	O	THR	A	609	-24.302	0.683	-8.247	1.00	19.06	A
ATOM	70	N	PHE	A	610	-22.925	-0.928	-7.524	1.00	18.09	A
ATOM	71	CA	PHE	A	610	-23.709	-1.967	-8.181	1.00	19.10	A
ATOM	72	CB	PHE	A	610	-22.955	-3.299	-8.223	1.00	20.69	A
ATOM	73	CG	PHE	A	610	-21.861	-3.357	-9.240	1.00	21.23	A
ATOM	74	CD1	PHE	A	610	-20.707	-2.610	-9.082	1.00	22.59	A
ATOM	75	CD2	PHE	A	610	-21.973	-4.184	-10.350	1.00	23.50	A
ATOM	76	CE1	PHE	A	610	-19.678	-2.681	-10.007	1.00	21.63	A
ATOM	77	CE2	PHE	A	610	-20.942	-4.261	-11.285	1.00	23.79	A
ATOM	78	CZ	PHE	A	610	-19.791	-3.504	-11.107	1.00	20.78	A

ATOM	79	C	PHE	A	610	-25.000	-2.167	-7.386	1.00	20.52	A
ATOM	80	O	PHE	A	610	-24.986	-2.148	-6.150	1.00	20.43	A
ATOM	81	N	GLU	A	611	-26.111	-2.343	-8.095	1.00	20.58	A
ATOM	82	CA	GLU	A	611	-27.404	-2.571	-7.459	1.00	21.53	A
ATOM	83	CB	GLU	A	611	-28.485	-2.853	-8.523	1.00	22.75	A
ATOM	84	CG	GLU	A	611	-28.714	-1.718	-9.518	0.00	23.28	A
ATOM	85	CD	GLU	A	611	-29.783	-2.041	-10.554	0.00	23.79	A
ATOM	86	OE1	GLU	A	611	-30.061	-1.175	-11.409	0.00	24.06	A
ATOM	87	OE2	GLU	A	611	-30.345	-3.158	-10.516	0.00	24.06	A
ATOM	88	C	GLU	A	611	-27.257	-3.790	-6.546	1.00	21.14	A
ATOM	89	O	GLU	A	611	-27.861	-3.857	-5.479	1.00	20.93	A
ATOM	90	N	ASP	A	612	-26.445	-4.746	-6.992	1.00	21.15	A
ATOM	91	CA	ASP	A	612	-26.160	-5.966	-6.239	1.00	21.15	A
ATOM	92	CB	ASP	A	612	-26.738	-7.203	-6.946	1.00	22.41	A
ATOM	93	CG	ASP	A	612	-26.407	-8.504	-6.220	1.00	26.34	A
ATOM	94	OD1	ASP	A	612	-25.869	-8.451	-5.091	1.00	26.08	A
ATOM	95	OD2	ASP	A	612	-26.693	-9.588	-6.776	1.00	28.73	A
ATOM	96	C	ASP	A	612	-24.641	-6.106	-6.114	1.00	20.74	A
ATOM	97	O	ASP	A	612	-23.967	-6.530	-7.051	1.00	18.43	A
ATOM	98	N	PRO	A	613	-24.085	-5.745	-4.948	1.00	22.26	A
ATOM	99	CD	PRO	A	613	-24.796	-5.172	-3.790	1.00	21.09	A
ATOM	100	CA	PRO	A	613	-22.642	-5.825	-4.692	1.00	23.09	A
ATOM	101	CB	PRO	A	613	-22.551	-5.579	-3.188	1.00	23.78	A
ATOM	102	CG	PRO	A	613	-23.662	-4.598	-2.957	1.00	24.95	A
ATOM	103	C	PRO	A	613	-22.001	-7.149	-5.112	1.00	24.21	A
ATOM	104	O	PRO	A	613	-20.830	-7.182	-5.486	1.00	24.14	A
ATOM	105	N	ASN	A	614	-22.764	-8.238	-5.060	1.00	24.32	A
ATOM	106	CA	ASN	A	614	-22.232	-9.544	-5.445	1.00	24.86	A
ATOM	107	CB	ASN	A	614	-23.242	-10.652	-5.162	1.00	28.16	A
ATOM	108	CG	ASN	A	614	-23.520	-10.813	-3.699	1.00	30.99	A
ATOM	109	OD1	ASN	A	614	-22.600	-10.994	-2.903	1.00	33.48	A
ATOM	110	ND2	ASN	A	614	-24.795	-10.750	-3.325	1.00	34.69	A
ATOM	111	C	ASN	A	614	-21.866	-9.598	-6.912	1.00	25.02	A
ATOM	112	O	ASN	A	614	-21.035	-10.412	-7.329	1.00	23.77	A
ATOM	113	N	GLU	A	615	-22.498	-8.742	-7.706	1.00	22.98	A
ATOM	114	CA	GLU	A	615	-22.213	-8.728	-9.129	1.00	23.04	A
ATOM	115	CB	GLU	A	615	-23.144	-7.762	-9.863	1.00	24.89	A
ATOM	116	CG	GLU	A	615	-22.838	-7.681	-11.345	1.00	29.63	A
ATOM	117	CD	GLU	A	615	-22.902	-9.036	-12.032	1.00	33.50	A
ATOM	118	OE1	GLU	A	615	-22.270	-9.188	-13.103	1.00	35.83	A
ATOM	119	OE2	GLU	A	615	-23.589	-9.949	-11.511	1.00	35.71	A
ATOM	120	C	GLU	A	615	-20.766	-8.312	-9.348	1.00	19.65	A
ATOM	121	O	GLU	A	615	-20.079	-8.854	-10.211	1.00	19.95	A
ATOM	122	N	ALA	A	616	-20.306	-7.340	-8.569	1.00	19.06	A
ATOM	123	CA	ALA	A	616	-18.932	-6.884	-8.702	1.00	16.63	A
ATOM	124	CB	ALA	A	616	-18.676	-5.728	-7.763	1.00	16.24	A
ATOM	125	C	ALA	A	616	-17.982	-8.037	-8.401	1.00	15.74	A
ATOM	126	O	ALA	A	616	-16.929	-8.180	-9.031	1.00	15.81	A
ATOM	127	N	VAL	A	617	-18.353	-8.880	-7.447	1.00	15.22	A
ATOM	128	CA	VAL	A	617	-17.493	-10.001	-7.106	1.00	14.30	A
ATOM	129	CB	VAL	A	617	-18.003	-10.750	-5.865	1.00	14.79	A
ATOM	130	CG1	VAL	A	617	-17.028	-11.869	-5.501	1.00	16.38	A
ATOM	131	CG2	VAL	A	617	-18.123	-9.781	-4.703	1.00	11.27	A
ATOM	132	C	VAL	A	617	-17.337	-10.979	-8.256	1.00	14.61	A
ATOM	133	O	VAL	A	617	-16.215	-11.372	-8.608	1.00	14.99	A
ATOM	134	N	ARG	A	618	-18.445	-11.370	-8.868	1.00	16.24	A
ATOM	135	CA	ARG	A	618	-18.353	-12.322	-9.964	1.00	18.27	A
ATOM	136	CB	ARG	A	618	-19.752	-12.808	-10.375	1.00	20.76	A
ATOM	137	CG	ARG	A	618	-20.691	-11.740	-10.838	0.00	21.07	A
ATOM	138	CD	ARG	A	618	-22.044	-12.351	-11.112	0.00	22.19	A
ATOM	139	NE	ARG	A	618	-22.650	-12.891	-9.899	0.00	22.97	A
ATOM	140	CZ	ARG	A	618	-23.853	-13.451	-9.857	0.00	23.42	A
ATOM	141	NH1	ARG	A	618	-24.575	-13.545	-10.965	0.00	23.69	A
ATOM	142	NH2	ARG	A	618	-24.342	-13.903	-8.711	0.00	23.69	A

ATOM	143	C	ARG	A	618	-17.626	-11.746	-11.168	1.00	18.93	A
ATOM	144	O	ARG	A	618	-16.988	-12.479	-11.928	1.00	21.33	A
ATOM	145	N	GLU	A	619	-17.707	-10.430	-11.334	1.00	18.93	A
ATOM	146	CA	GLU	A	619	-17.059	-9.777	-12.463	1.00	20.86	A
ATOM	147	CB	GLU	A	619	-17.728	-8.439	-12.745	1.00	23.33	A
ATOM	148	CG	GLU	A	619	-19.148	-8.576	-13.213	1.00	30.69	A
ATOM	149	CD	GLU	A	619	-19.640	-7.325	-13.876	1.00	34.05	A
ATOM	150	OE1	GLU	A	619	-20.842	-7.271	-14.214	1.00	37.39	A
ATOM	151	OE2	GLU	A	619	-18.821	-6.396	-14.065	1.00	36.23	A
ATOM	152	C	GLU	A	619	-15.564	-9.548	-12.338	1.00	20.77	A
ATOM	153	O	GLU	A	619	-14.829	-9.748	-13.300	1.00	21.23	A
ATOM	154	N	PHE	A	620	-15.113	-9.128	-11.161	1.00	19.38	A
ATOM	155	CA	PHE	A	620	-13.697	-8.841	-10.977	1.00	20.53	A
ATOM	156	CB	PHE	A	620	-13.544	-7.472	-10.326	1.00	19.14	A
ATOM	157	CG	PHE	A	620	-14.366	-6.393	-10.987	1.00	18.99	A
ATOM	158	CD1	PHE	A	620	-15.303	-5.672	-10.258	1.00	18.77	A
ATOM	159	CD2	PHE	A	620	-14.193	-6.091	-12.339	1.00	22.01	A
ATOM	160	CE1	PHE	A	620	-16.061	-4.661	-10.859	1.00	20.15	A
ATOM	161	CE2	PHE	A	620	-14.947	-5.082	-12.951	1.00	20.05	A
ATOM	162	CZ	PHE	A	620	-15.879	-4.369	-12.205	1.00	18.18	A
ATOM	163	C	PHE	A	620	-12.892	-9.871	-10.190	1.00	22.13	A
ATOM	164	O	PHE	A	620	-11.677	-9.719	-10.037	1.00	21.27	A
ATOM	165	N	ALA	A	621	-13.562	-10.915	-9.704	1.00	22.03	A
ATOM	166	CA	ALA	A	621	-12.906	-11.959	-8.922	1.00	23.00	A
ATOM	167	CB	ALA	A	621	-13.365	-11.873	-7.469	1.00	22.11	A
ATOM	168	C	ALA	A	621	-13.159	-13.368	-9.456	1.00	24.84	A
ATOM	169	O	ALA	A	621	-14.300	-13.748	-9.731	1.00	24.07	A
ATOM	170	N	LYS	A	622	-12.088	-14.146	-9.587	1.00	24.59	A
ATOM	171	CA	LYS	A	622	-12.195	-15.517	-10.074	1.00	26.44	A
ATOM	172	CB	LYS	A	622	-10.842	-16.000	-10.600	1.00	29.90	A
ATOM	173	CG	LYS	A	622	-10.862	-17.445	-11.086	1.00	34.03	A
ATOM	174	CD	LYS	A	622	-9.455	-18.030	-11.189	1.00	36.96	A
ATOM	175	CE	LYS	A	622	-8.623	-17.304	-12.231	1.00	39.89	A
ATOM	176	NZ	LYS	A	622	-7.211	-17.795	-12.281	1.00	41.83	A
ATOM	177	C	LYS	A	622	-12.647	-16.453	-8.956	1.00	26.32	A
ATOM	178	O	LYS	A	622	-12.038	-16.482	-7.885	1.00	25.37	A
ATOM	179	N	GLU	A	623	-13.713	-17.211	-9.202	1.00	25.42	A
ATOM	180	CA	GLU	A	623	-14.222	-18.161	-8.214	1.00	25.52	A
ATOM	181	CB	GLU	A	623	-15.657	-18.582	-8.566	1.00	26.37	A
ATOM	182	CG	GLU	A	623	-16.289	-19.613	-7.627	1.00	26.38	A
ATOM	183	CD	GLU	A	623	-16.521	-19.094	-6.212	1.00	28.72	A
ATOM	184	OE1	GLU	A	623	-16.905	-17.909	-6.053	1.00	28.21	A
ATOM	185	OE2	GLU	A	623	-16.328	-19.876	-5.253	1.00	29.13	A
ATOM	186	C	GLU	A	623	-13.302	-19.371	-8.231	1.00	24.77	A
ATOM	187	O	GLU	A	623	-13.131	-20.015	-9.261	1.00	25.82	A
ATOM	188	N	ILE	A	624	-12.686	-19.663	-7.094	1.00	26.18	A
ATOM	189	CA	ILE	A	624	-11.777	-20.798	-6.993	1.00	25.31	A
ATOM	190	CB	ILE	A	624	-10.466	-20.400	-6.263	1.00	25.34	A
ATOM	191	CG2	ILE	A	624	-9.588	-21.641	-6.048	1.00	23.96	A
ATOM	192	CG1	ILE	A	624	-9.730	-19.327	-7.070	1.00	24.39	A
ATOM	193	CD1	ILE	A	624	-8.450	-18.815	-6.426	1.00	25.55	A
ATOM	194	C	ILE	A	624	-12.427	-21.950	-6.236	1.00	25.18	A
ATOM	195	O	ILE	A	624	-13.012	-21.763	-5.170	1.00	25.10	A
ATOM	196	N	ASP	A	625	-12.324	-23.144	-6.801	1.00	26.96	A
ATOM	197	CA	ASP	A	625	-12.890	-24.323	-6.167	1.00	27.95	A
ATOM	198	CB	ASP	A	625	-12.781	-25.528	-7.089	1.00	30.55	A
ATOM	199	CG	ASP	A	625	-13.634	-26.679	-6.625	1.00	34.97	A
ATOM	200	OD1	ASP	A	625	-14.850	-26.648	-6.907	1.00	37.34	A
ATOM	201	OD2	ASP	A	625	-13.095	-27.597	-5.963	1.00	34.92	A
ATOM	202	C	ASP	A	625	-12.088	-24.580	-4.902	1.00	27.84	A
ATOM	203	O	ASP	A	625	-10.857	-24.583	-4.937	1.00	26.54	A
ATOM	204	N	ILE	A	626	-12.781	-24.807	-3.791	1.00	27.43	A
ATOM	205	CA	ILE	A	626	-12.111	-25.042	-2.518	1.00	28.27	A
ATOM	206	CB	ILE	A	626	-13.149	-25.293	-1.398	1.00	29.15	A

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ATOM    207  CG2 ILE A 626     -13.897 -26.591  -1.660  1.00 28.78      A
ATOM    208  CG1 ILE A 626     -12.455 -25.330  -0.040  1.00 30.32      A
ATOM    209  CD1 ILE A 626     -13.412 -25.148   1.122  1.00 35.27      A
ATOM    210  C   ILE A 626     -11.099 -26.195  -2.563  1.00 27.88      A
ATOM    211  O   ILE A 626     -10.116 -26.198  -1.825  1.00 27.54      A
ATOM    212  N   SER A 627     -11.319 -27.164  -3.442  1.00 29.17      A
ATOM    213  CA  SER A 627     -10.393 -28.289  -3.538  1.00 29.60      A
ATOM    214  CB  SER A 627     -10.942 -29.350  -4.483  1.00 29.57      A
ATOM    215  OG  SER A 627     -10.885 -28.887  -5.818  1.00 31.25      A
ATOM    216  C   SER A 627      -9.009 -27.858  -4.028  1.00 29.72      A
ATOM    217  O   SER A 627      -8.072 -28.657  -4.025  1.00 29.55      A
ATOM    218  N   CYS A 628      -8.888 -26.606  -4.465  1.00 29.03      A
ATOM    219  CA  CYS A 628      -7.616 -26.075  -4.951  1.00 29.50      A
ATOM    220  CB  CYS A 628      -7.840 -25.103  -6.128  1.00 28.94      A
ATOM    221  SG  CYS A 628      -8.593 -25.809  -7.641  1.00 30.55      A
ATOM    222  C   CYS A 628      -6.871 -25.335  -3.836  1.00 29.48      A
ATOM    223  O   CYS A 628      -5.665 -25.115  -3.928  1.00 28.60      A
ATOM    224  N   VAL A 629      -7.592 -24.955  -2.785  1.00 30.83      A
ATOM    225  CA  VAL A 629      -7.004 -24.218  -1.671  1.00 31.02      A
ATOM    226  CB  VAL A 629      -7.999 -23.159  -1.128  1.00 32.23      A
ATOM    227  CG1 VAL A 629      -7.317 -22.303  -0.052  1.00 32.29      A
ATOM    228  CG2 VAL A 629      -8.509 -22.280  -2.264  1.00 31.46      A
ATOM    229  C   VAL A 629      -6.578 -25.107  -0.498  1.00 32.09      A
ATOM    230  O   VAL A 629      -7.324 -25.985  -0.063  1.00 32.06      A
ATOM    231  N   LYS A 630      -5.377 -24.869   0.017  1.00 31.20      A
ATOM    232  CA  LYS A 630      -4.889 -25.641   1.148  1.00 32.57      A
ATOM    233  CB  LYS A 630      -3.847 -26.667   0.686  1.00 32.81      A
ATOM    234  CG  LYS A 630      -4.348 -27.600  -0.410  0.00 33.76      A
ATOM    235  CD  LYS A 630      -3.253 -28.548  -0.871  0.00 34.37      A
ATOM    236  CE  LYS A 630      -3.749 -29.493  -1.955  0.00 34.80      A
ATOM    237  NZ  LYS A 630      -4.215 -28.765  -3.167  0.00 35.13      A
ATOM    238  C   LYS A 630      -4.286 -24.708   2.190  1.00 31.65      A
ATOM    239  O   LYS A 630      -3.204 -24.162   2.000  1.00 31.96      A
ATOM    240  N   ILE A 631      -5.009 -24.513   3.285  1.00 32.38      A
ATOM    241  CA  ILE A 631      -4.542 -23.655   4.359  1.00 33.62      A
ATOM    242  CB  ILE A 631      -5.700 -23.282   5.314  1.00 33.44      A
ATOM    243  CG2 ILE A 631      -5.155 -22.539   6.532  1.00 33.62      A
ATOM    244  CG1 ILE A 631      -6.740 -22.438   4.565  1.00 33.30      A
ATOM    245  CD1 ILE A 631      -7.916 -21.992   5.416  1.00 31.54      A
ATOM    246  C   ILE A 631      -3.464 -24.396   5.142  1.00 34.94      A
ATOM    247  O   ILE A 631      -3.709 -25.490   5.646  1.00 34.77      A
ATOM    248  N   GLU A 632      -2.278 -23.797   5.237  1.00 35.73      A
ATOM    249  CA  GLU A 632      -1.154 -24.396   5.958  1.00 37.69      A
ATOM    250  CB  GLU A 632       0.167 -24.114   5.236  1.00 38.83      A
ATOM    251  CG  GLU A 632       0.312 -24.785   3.892  0.00 39.80      A
ATOM    252  CD  GLU A 632       0.374 -26.290   4.006  0.00 40.38      A
ATOM    253  OE1 GLU A 632       1.254 -26.793   4.735  0.00 40.70      A
ATOM    254  OE2 GLU A 632      -0.455 -26.970   3.367  0.00 40.70      A
ATOM    255  C   GLU A 632      -1.047 -23.892   7.394  1.00 38.57      A
ATOM    256  O   GLU A 632      -1.118 -24.681   8.342  1.00 38.93      A
ATOM    257  N   GLN A 633      -0.868 -22.583   7.556  1.00 38.28      A
ATOM    258  CA  GLN A 633      -0.744 -21.995   8.889  1.00 39.08      A
ATOM    259  CB  GLN A 633       0.739 -21.825   9.250  1.00 40.39      A
ATOM    260  CG  GLN A 633       1.001 -21.482  10.712  0.00 41.11      A
ATOM    261  CD  GLN A 633       2.481 -21.367  11.028  0.00 41.66      A
ATOM    262  OE1 GLN A 633       3.235 -22.331  10.891  0.00 41.94      A
ATOM    263  NE2 GLN A 633       2.904 -20.183  11.455  0.00 41.94      A
ATOM    264  C   GLN A 633      -1.455 -20.650   8.994  1.00 39.45      A
ATOM    265  O   GLN A 633      -1.725 -20.000   7.982  1.00 36.93      A
ATOM    266  N   VAL A 634      -1.762 -20.238  10.221  1.00 39.17      A
ATOM    267  CA  VAL A 634      -2.425 -18.960  10.445  1.00 41.26      A
ATOM    268  CB  VAL A 634      -3.371 -19.013  11.653  1.00 41.53      A
ATOM    269  CG1 VAL A 634      -4.109 -17.694  11.778  1.00 42.05      A
ATOM    270  CG2 VAL A 634      -4.344 -20.164  11.501  1.00 40.57      A
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ATOM    271  C   VAL A 634      -1.368 -17.900  10.719  1.00 42.58      A
ATOM    272  O   VAL A 634      -0.569 -18.044  11.649  1.00 43.99      A
ATOM    273  N   ILE A 635      -1.365 -16.842   9.910  1.00 43.60      A
ATOM    274  CA  ILE A 635      -0.398 -15.749  10.045  1.00 44.51      A
ATOM    275  CB  ILE A 635      -0.214 -14.995   8.699  1.00 45.18      A
ATOM    276  CG2 ILE A 635       0.860 -13.925   8.841  0.00 45.30      A
ATOM    277  CG1 ILE A 635       0.154 -15.979   7.586  0.00 45.40      A
ATOM    278  CD1 ILE A 635       1.450 -16.730   7.817  0.00 45.70      A
ATOM    279  C   ILE A 635      -0.846 -14.744  11.103  1.00 45.18      A
ATOM    280  O   ILE A 635      -0.281 -14.678  12.197  1.00 45.07      A
ATOM    281  N   GLY A 636      -1.871 -13.966  10.768  1.00 45.30      A
ATOM    282  CA  GLY A 636      -2.385 -12.968  11.689  1.00 45.00      A
ATOM    283  C   GLY A 636      -3.900 -12.992  11.798  1.00 44.80      A
ATOM    284  O   GLY A 636      -4.550 -13.951  11.375  1.00 44.35      A
ATOM    285  N   ALA A 637      -4.462 -11.934  12.373  1.00 44.33      A
ATOM    286  CA  ALA A 637      -5.906 -11.818  12.545  1.00 43.81      A
ATOM    287  CB  ALA A 637      -6.238 -11.493  13.996  1.00 43.88      A
ATOM    288  C   ALA A 637      -6.450 -10.729  11.634  1.00 43.58      A
ATOM    289  O   ALA A 637      -5.828  -9.677  11.465  1.00 42.65      A
ATOM    290  N   GLY A 638      -7.612 -10.988  11.044  1.00 43.24      A
ATOM    291  CA  GLY A 638      -8.218 -10.012  10.157  1.00 41.84      A
ATOM    292  C   GLY A 638      -9.481  -9.419  10.741  1.00 41.01      A
ATOM    293  O   GLY A 638      -9.978  -9.880  11.773  1.00 41.22      A
ATOM    294  N   GLU A 639     -10.006  -8.397  10.075  1.00 40.04      A
ATOM    295  CA  GLU A 639     -11.222  -7.733  10.525  1.00 37.62      A
ATOM    296  CB  GLU A 639     -11.469  -6.470   9.695  1.00 39.78      A
ATOM    297  CG  GLU A 639     -12.702  -5.688  10.127  1.00 44.07      A
ATOM    298  CD  GLU A 639     -13.102  -4.611   9.134  1.00 46.08      A
ATOM    299  OE1 GLU A 639     -14.145  -3.961   9.358  1.00 48.25      A
ATOM    300  OE2 GLU A 639     -12.381  -4.416   8.128  1.00 47.68      A
ATOM    301  C   GLU A 639     -12.448  -8.645  10.431  1.00 35.13      A
ATOM    302  O   GLU A 639     -13.392  -8.509  11.219  1.00 34.00      A
ATOM    303  N   PHE A 640     -12.430  -9.574   9.477  1.00 31.83      A
ATOM    304  CA  PHE A 640     -13.560 -10.482   9.278  1.00 30.48      A
ATOM    305  CB  PHE A 640     -14.083 -10.366   7.832  1.00 29.76      A
ATOM    306  CG  PHE A 640     -14.482  -8.966   7.433  1.00 28.46      A
ATOM    307  CD1 PHE A 640     -13.531  -8.058   6.974  1.00 28.70      A
ATOM    308  CD2 PHE A 640     -15.802  -8.545   7.548  1.00 28.68      A
ATOM    309  CE1 PHE A 640     -13.889  -6.745   6.636  1.00 27.42      A
ATOM    310  CE2 PHE A 640     -16.172  -7.237   7.215  1.00 26.96      A
ATOM    311  CZ  PHE A 640     -15.211  -6.337   6.759  1.00 27.64      A
ATOM    312  C   PHE A 640     -13.242 -11.952   9.591  1.00 29.44      A
ATOM    313  O   PHE A 640     -14.118 -12.817   9.499  1.00 27.82      A
ATOM    314  N   GLY A 641     -11.998 -12.230   9.966  1.00 28.09      A
ATOM    315  CA  GLY A 641     -11.611 -13.597  10.266  1.00 28.09      A
ATOM    316  C   GLY A 641     -10.105 -13.766  10.389  1.00 28.66      A
ATOM    317  O   GLY A 641      -9.402 -12.833  10.777  1.00 27.98      A
ATOM    318  N   GLU A 642      -9.609 -14.955  10.052  1.00 27.87      A
ATOM    319  CA  GLU A 642      -8.185 -15.249  10.140  1.00 28.48      A
ATOM    320  CB  GLU A 642      -7.969 -16.715  10.559  1.00 31.49      A
ATOM    321  CG  GLU A 642      -8.655 -17.116  11.879  1.00 35.67      A
ATOM    322  CD  GLU A 642      -8.289 -18.526  12.345  1.00 38.58      A
ATOM    323  OE1 GLU A 642      -8.407 -19.482  11.544  1.00 39.58      A
ATOM    324  OE2 GLU A 642      -7.884 -18.676  13.521  1.00 39.80      A
ATOM    325  C   GLU A 642      -7.419 -14.989   8.844  1.00 27.74      A
ATOM    326  O   GLU A 642      -7.980 -15.043   7.744  1.00 26.91      A
ATOM    327  N   VAL A 643      -6.130 -14.693   8.989  1.00 27.11      A
ATOM    328  CA  VAL A 643      -5.252 -14.461   7.853  1.00 26.42      A
ATOM    329  CB  VAL A 643      -4.478 -13.134   7.996  1.00 25.95      A
ATOM    330  CG1 VAL A 643      -3.732 -12.838   6.728  1.00 25.98      A
ATOM    331  CG2 VAL A 643      -5.427 -12.014   8.334  1.00 25.96      A
ATOM    332  C   VAL A 643      -4.268 -15.620   7.891  1.00 26.37      A
ATOM    333  O   VAL A 643      -3.519 -15.763   8.858  1.00 24.39      A
ATOM    334  N   CYS A 644      -4.267 -16.433   6.836  1.00 25.63      A
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ATOM	335	CA	CYS	A	644	-3.409	-17.616	6.763	1.00	25.19	A
ATOM	336	CB	CYS	A	644	-4.275	-18.883	6.718	1.00	25.46	A
ATOM	337	SG	CYS	A	644	-5.746	-18.849	7.750	1.00	28.36	A
ATOM	338	C	CYS	A	644	-2.483	-17.655	5.551	1.00	25.37	A
ATOM	339	O	CYS	A	644	-2.556	-16.811	4.657	1.00	25.07	A
ATOM	340	N	SER	A	645	-1.615	-18.658	5.532	1.00	23.66	A
ATOM	341	CA	SER	A	645	-0.709	-18.873	4.419	1.00	24.21	A
ATOM	342	CB	SER	A	645	0.750	-18.801	4.862	1.00	24.10	A
ATOM	343	OG	SER	A	645	1.107	-19.968	5.574	1.00	27.96	A
ATOM	344	C	SER	A	645	-1.025	-20.280	3.949	1.00	23.74	A
ATOM	345	O	SER	A	645	-1.558	-21.088	4.715	1.00	22.82	A
ATOM	346	N	GLY	A	646	-0.703	-20.575	2.695	1.00	24.19	A
ATOM	347	CA	GLY	A	646	-0.985	-21.898	2.171	1.00	22.79	A
ATOM	348	C	GLY	A	646	-0.559	-22.070	0.730	1.00	22.27	A
ATOM	349	O	GLY	A	646	0.255	-21.304	0.208	1.00	21.87	A
ATOM	350	N	HIS	A	647	-1.097	-23.100	0.091	1.00	22.58	A
ATOM	351	CA	HIS	A	647	-0.776	-23.367	-1.296	1.00	24.03	A
ATOM	352	CB	HIS	A	647	-0.024	-24.698	-1.445	1.00	25.12	A
ATOM	353	CG	HIS	A	647	1.316	-24.725	-0.770	1.00	27.93	A
ATOM	354	CD2	HIS	A	647	2.572	-24.751	-1.278	1.00	28.54	A
ATOM	355	ND1	HIS	A	647	1.460	-24.753	0.602	1.00	29.81	A
ATOM	356	CE1	HIS	A	647	2.745	-24.800	0.909	1.00	28.73	A
ATOM	357	NE2	HIS	A	647	3.441	-24.799	-0.214	1.00	30.01	A
ATOM	358	C	HIS	A	647	-2.054	-23.392	-2.125	1.00	22.29	A
ATOM	359	O	HIS	A	647	-3.134	-23.758	-1.643	1.00	22.95	A
ATOM	360	N	LEU	A	648	-1.913	-22.977	-3.376	1.00	22.24	A
ATOM	361	CA	LEU	A	648	-3.010	-22.935	-4.323	1.00	22.62	A
ATOM	362	CB	LEU	A	648	-3.302	-21.488	-4.743	1.00	22.09	A
ATOM	363	CG	LEU	A	648	-4.285	-21.306	-5.898	1.00	21.11	A
ATOM	364	CD1	LEU	A	648	-5.639	-21.893	-5.505	1.00	22.47	A
ATOM	365	CD2	LEU	A	648	-4.418	-19.834	-6.250	1.00	21.63	A
ATOM	366	C	LEU	A	648	-2.565	-23.737	-5.532	1.00	24.96	A
ATOM	367	O	LEU	A	648	-1.525	-23.447	-6.131	1.00	25.51	A
ATOM	368	N	LYS	A	649	-3.343	-24.755	-5.879	1.00	27.46	A
ATOM	369	CA	LYS	A	649	-3.029	-25.596	-7.024	1.00	31.13	A
ATOM	370	CB	LYS	A	649	-2.997	-27.078	-6.610	1.00	31.15	A
ATOM	371	CG	LYS	A	649	-2.185	-27.994	-7.529	0.00	31.95	A
ATOM	372	CD	LYS	A	649	-2.818	-28.177	-8.903	0.00	32.48	A
ATOM	373	CE	LYS	A	649	-1.940	-29.047	-9.801	0.00	32.88	A
ATOM	374	NZ	LYS	A	649	-1.650	-30.379	-9.199	0.00	33.21	A
ATOM	375	C	LYS	A	649	-4.115	-25.373	-8.066	1.00	33.65	A
ATOM	376	O	LYS	A	649	-5.272	-25.744	-7.858	1.00	35.71	A
ATOM	377	N	LEU	A	650	-3.740	-24.753	-9.178	1.00	35.03	A
ATOM	378	CA	LEU	A	650	-4.681	-24.498	-10.265	1.00	36.97	A
ATOM	379	CB	LEU	A	650	-4.654	-23.021	-10.659	1.00	36.46	A
ATOM	380	CG	LEU	A	650	-5.111	-22.027	-9.592	1.00	37.31	A
ATOM	381	CD1	LEU	A	650	-4.809	-20.616	-10.058	1.00	37.80	A
ATOM	382	CD2	LEU	A	650	-6.596	-22.211	-9.307	1.00	35.30	A
ATOM	383	C	LEU	A	650	-4.308	-25.361	-11.465	1.00	36.94	A
ATOM	384	O	LEU	A	650	-3.274	-26.027	-11.458	1.00	35.61	A
ATOM	385	N	ARG	A	654	1.042	-25.384	-11.878	1.00	38.79	A
ATOM	386	CA	ARG	A	654	1.946	-25.673	-10.770	1.00	38.06	A
ATOM	387	CB	ARG	A	654	3.360	-25.184	-11.092	1.00	40.05	A
ATOM	388	CG	ARG	A	654	4.377	-25.516	-10.010	0.00	40.81	A
ATOM	389	CD	ARG	A	654	5.712	-24.843	-10.271	0.00	41.95	A
ATOM	390	NE	ARG	A	654	6.674	-25.111	-9.205	0.00	42.83	A
ATOM	391	CZ	ARG	A	654	7.878	-24.553	-9.127	0.00	43.31	A
ATOM	392	NH1	ARG	A	654	8.273	-23.692	-10.055	0.00	43.60	A
ATOM	393	NH2	ARG	A	654	8.687	-24.854	-8.121	0.00	43.60	A
ATOM	394	C	ARG	A	654	1.477	-25.019	-9.473	1.00	36.96	A
ATOM	395	O	ARG	A	654	0.953	-23.905	-9.479	1.00	37.48	A
ATOM	396	N	GLU	A	655	1.677	-25.718	-8.360	1.00	34.47	A
ATOM	397	CA	GLU	A	655	1.279	-25.210	-7.055	1.00	32.62	A
ATOM	398	CB	GLU	A	655	1.489	-26.287	-5.995	1.00	34.16	A

ATOM	399	CG	GLU	A	655	0.948	-25.911	-4.628	1.00	37.34	A
ATOM	400	CD	GLU	A	655	1.042	-27.056	-3.638	1.00	39.34	A
ATOM	401	OE1	GLU	A	655	2.177	-27.464	-3.306	1.00	40.30	A
ATOM	402	OE2	GLU	A	655	-0.017	-27.547	-3.200	1.00	40.82	A
ATOM	403	C	GLU	A	655	2.075	-23.963	-6.672	1.00	30.39	A
ATOM	404	O	GLU	A	655	3.263	-23.864	-6.970	1.00	30.59	A
ATOM	405	N	ILE	A	656	1.417	-23.006	-6.024	1.00	26.58	A
ATOM	406	CA	ILE	A	656	2.096	-21.787	-5.599	1.00	24.21	A
ATOM	407	CB	ILE	A	656	1.779	-20.575	-6.522	1.00	22.73	A
ATOM	408	CG2	ILE	A	656	2.273	-20.843	-7.949	1.00	21.90	A
ATOM	409	CG1	ILE	A	656	0.271	-20.283	-6.494	1.00	22.82	A
ATOM	410	CD1	ILE	A	656	-0.124	-18.937	-7.096	1.00	20.25	A
ATOM	411	C	ILE	A	656	1.680	-21.399	-4.185	1.00	22.57	A
ATOM	412	O	ILE	A	656	0.593	-21.758	-3.731	1.00	21.28	A
ATOM	413	N	PHE	A	657	2.552	-20.669	-3.493	1.00	22.56	A
ATOM	414	CA	PHE	A	657	2.251	-20.190	-2.147	1.00	21.07	A
ATOM	415	CB	PHE	A	657	3.516	-19.648	-1.462	1.00	27.21	A
ATOM	416	CG	PHE	A	657	4.424	-20.719	-0.909	1.00	32.40	A
ATOM	417	CD1	PHE	A	657	5.499	-21.203	-1.652	1.00	36.01	A
ATOM	418	CD2	PHE	A	657	4.188	-21.258	0.355	1.00	35.51	A
ATOM	419	CE1	PHE	A	657	6.327	-22.209	-1.144	1.00	36.52	A
ATOM	420	CE2	PHE	A	657	5.009	-22.265	0.872	1.00	37.58	A
ATOM	421	CZ	PHE	A	657	6.080	-22.740	0.120	1.00	37.93	A
ATOM	422	C	PHE	A	657	1.240	-19.054	-2.292	1.00	20.47	A
ATOM	423	O	PHE	A	657	1.295	-18.298	-3.261	1.00	19.30	A
ATOM	424	N	VAL	A	658	0.314	-18.941	-1.347	1.00	17.78	A
ATOM	425	CA	VAL	A	658	-0.676	-17.873	-1.392	1.00	16.97	A
ATOM	426	CB	VAL	A	658	-2.004	-18.311	-2.112	1.00	15.03	A
ATOM	427	CG1	VAL	A	658	-1.779	-18.443	-3.615	1.00	13.58	A
ATOM	428	CG2	VAL	A	658	-2.504	-19.636	-1.546	1.00	17.13	A
ATOM	429	C	VAL	A	658	-1.034	-17.421	0.012	1.00	17.80	A
ATOM	430	O	VAL	A	658	-0.782	-18.140	0.990	1.00	16.73	A
ATOM	431	N	ALA	A	659	-1.596	-16.218	0.102	1.00	14.11	A
ATOM	432	CA	ALA	A	659	-2.060	-15.671	1.367	1.00	15.67	A
ATOM	433	CB	ALA	A	659	-1.810	-14.162	1.433	1.00	14.67	A
ATOM	434	C	ALA	A	659	-3.552	-15.965	1.283	1.00	16.07	A
ATOM	435	O	ALA	A	659	-4.150	-15.830	0.207	1.00	16.48	A
ATOM	436	N	ILE	A	660	-4.145	-16.377	2.401	1.00	17.28	A
ATOM	437	CA	ILE	A	660	-5.557	-16.756	2.453	1.00	20.16	A
ATOM	438	CB	ILE	A	660	-5.691	-18.307	2.608	1.00	20.13	A
ATOM	439	CG2	ILE	A	660	-7.149	-18.725	2.565	1.00	22.79	A
ATOM	440	CG1	ILE	A	660	-4.938	-19.019	1.483	1.00	21.87	A
ATOM	441	CD1	ILE	A	660	-4.887	-20.538	1.654	1.00	22.50	A
ATOM	442	C	ILE	A	660	-6.309	-16.101	3.609	1.00	22.05	A
ATOM	443	O	ILE	A	660	-5.937	-16.254	4.774	1.00	22.45	A
ATOM	444	N	LYS	A	661	-7.367	-15.372	3.274	1.00	22.33	A
ATOM	445	CA	LYS	A	661	-8.201	-14.707	4.267	1.00	23.44	A
ATOM	446	CB	LYS	A	661	-8.507	-13.270	3.850	1.00	26.63	A
ATOM	447	CG	LYS	A	661	-7.426	-12.272	4.175	1.00	30.21	A
ATOM	448	CD	LYS	A	661	-7.924	-10.863	3.894	1.00	32.40	A
ATOM	449	CE	LYS	A	661	-6.980	-9.824	4.450	1.00	34.22	A
ATOM	450	NZ	LYS	A	661	-7.561	-8.466	4.315	1.00	34.03	A
ATOM	451	C	LYS	A	661	-9.509	-15.479	4.376	1.00	23.79	A
ATOM	452	O	LYS	A	661	-10.109	-15.837	3.366	1.00	22.44	A
ATOM	453	N	THR	A	662	-9.940	-15.751	5.599	1.00	22.77	A
ATOM	454	CA	THR	A	662	-11.174	-16.485	5.800	1.00	23.53	A
ATOM	455	CB	THR	A	662	-10.938	-17.758	6.637	1.00	25.15	A
ATOM	456	OG1	THR	A	662	-10.286	-17.399	7.860	1.00	26.34	A
ATOM	457	CG2	THR	A	662	-10.065	-18.748	5.872	1.00	25.34	A
ATOM	458	C	THR	A	662	-12.183	-15.608	6.518	1.00	24.19	A
ATOM	459	O	THR	A	662	-11.814	-14.694	7.256	1.00	25.54	A
ATOM	460	N	LEU	A	663	-13.459	-15.887	6.282	1.00	24.00	A
ATOM	461	CA	LEU	A	663	-14.542	-15.146	6.904	1.00	26.09	A
ATOM	462	CB	LEU	A	663	-15.667	-14.907	5.887	1.00	23.14	A

ATOM	463	CG	LEU	A	663	-16.886	-14.132	6.383	1.00	24.98	A
ATOM	464	CD1	LEU	A	663	-16.448	-12.756	6.855	1.00	22.54	A
ATOM	465	CD2	LEU	A	663	-17.931	-14.012	5.263	1.00	23.69	A
ATOM	466	C	LEU	A	663	-15.067	-15.977	8.076	1.00	27.30	A
ATOM	467	O	LEU	A	663	-15.493	-17.115	7.888	1.00	28.82	A
ATOM	468	N	LYS	A	664	-15.026	-15.401	9.275	1.00	28.84	A
ATOM	469	CA	LYS	A	664	-15.490	-16.061	10.490	1.00	30.02	A
ATOM	470	CB	LYS	A	664	-15.417	-15.086	11.674	1.00	31.14	A
ATOM	471	CG	LYS	A	664	-16.325	-13.865	11.549	0.00	31.57	A
ATOM	472	CD	LYS	A	664	-16.193	-12.935	12.752	0.00	32.18	A
ATOM	473	CE	LYS	A	664	-17.158	-11.760	12.657	0.00	32.50	A
ATOM	474	NZ	LYS	A	664	-16.945	-10.972	11.413	0.00	32.80	A
ATOM	475	C	LYS	A	664	-16.923	-16.572	10.334	1.00	30.86	A
ATOM	476	O	LYS	A	664	-17.802	-15.841	9.880	1.00	31.20	A
ATOM	477	N	SER	A	665	-17.152	-17.829	10.711	1.00	31.16	A
ATOM	478	CA	SER	A	665	-18.479	-18.439	10.628	1.00	30.42	A
ATOM	479	CB	SER	A	665	-18.431	-19.861	11.178	1.00	32.90	A
ATOM	480	OG	SER	A	665	-18.013	-19.840	12.532	1.00	35.02	A
ATOM	481	C	SER	A	665	-19.487	-17.629	11.439	1.00	30.07	A
ATOM	482	O	SER	A	665	-19.128	-17.026	12.455	1.00	29.38	A
ATOM	483	N	GLY	A	666	-20.743	-17.622	10.993	1.00	28.66	A
ATOM	484	CA	GLY	A	666	-21.781	-16.876	11.689	1.00	27.97	A
ATOM	485	C	GLY	A	666	-21.789	-15.423	11.250	1.00	27.26	A
ATOM	486	O	GLY	A	666	-22.273	-14.535	11.958	1.00	25.74	A
ATOM	487	N	TYR	A	667	-21.239	-15.186	10.065	1.00	27.08	A
ATOM	488	CA	TYR	A	667	-21.156	-13.847	9.494	1.00	25.72	A
ATOM	489	CB	TYR	A	667	-20.169	-13.854	8.325	1.00	25.23	A
ATOM	490	CG	TYR	A	667	-20.563	-14.793	7.207	1.00	24.76	A
ATOM	491	CD1	TYR	A	667	-21.567	-14.447	6.301	1.00	23.91	A
ATOM	492	CE1	TYR	A	667	-21.951	-15.314	5.284	1.00	25.60	A
ATOM	493	CD2	TYR	A	667	-19.947	-16.040	7.067	1.00	23.97	A
ATOM	494	CE2	TYR	A	667	-20.323	-16.917	6.051	1.00	25.46	A
ATOM	495	CZ	TYR	A	667	-21.325	-16.546	5.163	1.00	26.43	A
ATOM	496	OH	TYR	A	667	-21.691	-17.392	4.143	1.00	28.78	A
ATOM	497	C	TYR	A	667	-22.515	-13.345	9.004	1.00	25.35	A
ATOM	498	O	TYR	A	667	-23.358	-14.125	8.569	1.00	24.49	A
ATOM	499	N	THR	A	668	-22.720	-12.037	9.081	1.00	24.59	A
ATOM	500	CA	THR	A	668	-23.963	-11.444	8.612	1.00	24.16	A
ATOM	501	CB	THR	A	668	-24.265	-10.131	9.344	1.00	25.06	A
ATOM	502	OG1	THR	A	668	-23.182	-9.209	9.132	1.00	28.51	A
ATOM	503	CG2	THR	A	668	-24.432	-10.381	10.837	1.00	24.37	A
ATOM	504	C	THR	A	668	-23.801	-11.147	7.119	1.00	24.62	A
ATOM	505	O	THR	A	668	-22.689	-11.224	6.585	1.00	21.64	A
ATOM	506	N	GLU	A	669	-24.908	-10.809	6.459	1.00	22.42	A
ATOM	507	CA	GLU	A	669	-24.901	-10.493	5.031	1.00	23.71	A
ATOM	508	CB	GLU	A	669	-26.315	-10.102	4.578	1.00	24.53	A
ATOM	509	CG	GLU	A	669	-26.450	-9.796	3.099	0.00	25.34	A
ATOM	510	CD	GLU	A	669	-26.084	-10.978	2.226	0.00	25.88	A
ATOM	511	OE1	GLU	A	669	-26.743	-12.033	2.345	0.00	26.22	A
ATOM	512	OE2	GLU	A	669	-25.137	-10.853	1.422	0.00	26.22	A
ATOM	513	C	GLU	A	669	-23.926	-9.351	4.744	1.00	21.59	A
ATOM	514	O	GLU	A	669	-23.152	-9.408	3.797	1.00	23.09	A
ATOM	515	N	LYS	A	670	-23.956	-8.329	5.589	1.00	22.19	A
ATOM	516	CA	LYS	A	670	-23.092	-7.171	5.439	1.00	20.44	A
ATOM	517	CB	LYS	A	670	-23.522	-6.073	6.415	1.00	19.94	A
ATOM	518	CG	LYS	A	670	-22.615	-4.846	6.417	1.00	19.99	A
ATOM	519	CD	LYS	A	670	-23.150	-3.762	7.315	1.00	19.07	A
ATOM	520	CE	LYS	A	670	-22.130	-2.654	7.524	1.00	21.46	A
ATOM	521	NZ	LYS	A	670	-21.542	-2.169	6.255	1.00	21.44	A
ATOM	522	C	LYS	A	670	-21.622	-7.527	5.668	1.00	22.01	A
ATOM	523	O	LYS	A	670	-20.750	-7.100	4.913	1.00	18.77	A
ATOM	524	N	GLN	A	671	-21.339	-8.305	6.707	1.00	20.25	A
ATOM	525	CA	GLN	A	671	-19.957	-8.678	6.969	1.00	21.57	A
ATOM	526	CB	GLN	A	671	-19.857	-9.540	8.226	1.00	19.59	A

ATOM	527	CG	GLN	A	671	-20.174	-8.772	9.489	1.00	23.04	A
ATOM	528	CD	GLN	A	671	-20.090	-9.646	10.715	1.00	23.12	A
ATOM	529	OE1	GLN	A	671	-20.591	-10.765	10.716	1.00	25.03	A
ATOM	530	NE2	GLN	A	671	-19.454	-9.141	11.766	1.00	26.08	A
ATOM	531	C	GLN	A	671	-19.360	-9.412	5.774	1.00	19.09	A
ATOM	532	O	GLN	A	671	-18.203	-9.188	5.419	1.00	19.45	A
ATOM	533	N	ARG	A	672	-20.159	-10.263	5.143	1.00	17.49	A
ATOM	534	CA	ARG	A	672	-19.711	-11.014	3.978	1.00	18.83	A
ATOM	535	CB	ARG	A	672	-20.775	-12.044	3.584	1.00	18.14	A
ATOM	536	CG	ARG	A	672	-20.482	-12.799	2.295	1.00	19.76	A
ATOM	537	CD	ARG	A	672	-21.620	-13.754	1.961	1.00	21.40	A
ATOM	538	NE	ARG	A	672	-21.459	-14.337	0.633	1.00	23.81	A
ATOM	539	CZ	ARG	A	672	-21.574	-13.656	-0.506	1.00	23.75	A
ATOM	540	NH1	ARG	A	672	-21.863	-12.361	-0.486	1.00	24.13	A
ATOM	541	NH2	ARG	A	672	-21.377	-14.267	-1.665	1.00	23.85	A
ATOM	542	C	ARG	A	672	-19.461	-10.053	2.813	1.00	19.29	A
ATOM	543	O	ARG	A	672	-18.476	-10.172	2.080	1.00	17.76	A
ATOM	544	N	ARG	A	673	-20.376	-9.102	2.655	1.00	19.04	A
ATOM	545	CA	ARG	A	673	-20.280	-8.113	1.592	1.00	18.53	A
ATOM	546	CB	ARG	A	673	-21.499	-7.192	1.599	1.00	16.97	A
ATOM	547	CG	ARG	A	673	-21.472	-6.171	0.481	1.00	16.95	A
ATOM	548	CD	ARG	A	673	-22.763	-5.428	0.403	1.00	18.42	A
ATOM	549	NE	ARG	A	673	-22.963	-4.625	1.595	1.00	23.56	A
ATOM	550	CZ	ARG	A	673	-24.042	-4.692	2.366	1.00	20.84	A
ATOM	551	NH1	ARG	A	673	-25.022	-5.533	2.066	1.00	22.79	A
ATOM	552	NH2	ARG	A	673	-24.140	-3.912	3.434	1.00	21.92	A
ATOM	553	C	ARG	A	673	-19.028	-7.269	1.740	1.00	17.35	A
ATOM	554	O	ARG	A	673	-18.245	-7.137	0.802	1.00	18.98	A
ATOM	555	N	ASP	A	674	-18.852	-6.678	2.915	1.00	15.56	A
ATOM	556	CA	ASP	A	674	-17.690	-5.846	3.151	1.00	17.33	A
ATOM	557	CB	ASP	A	674	-17.810	-5.182	4.527	1.00	18.55	A
ATOM	558	CG	ASP	A	674	-19.012	-4.227	4.609	1.00	22.12	A
ATOM	559	OD1	ASP	A	674	-19.522	-3.825	3.542	1.00	19.41	A
ATOM	560	OD2	ASP	A	674	-19.441	-3.870	5.722	1.00	23.46	A
ATOM	561	C	ASP	A	674	-16.376	-6.635	2.991	1.00	16.55	A
ATOM	562	O	ASP	A	674	-15.400	-6.145	2.412	1.00	14.92	A
ATOM	563	N	PHE	A	675	-16.362	-7.864	3.476	1.00	14.43	A
ATOM	564	CA	PHE	A	675	-15.190	-8.711	3.345	1.00	15.13	A
ATOM	565	CB	PHE	A	675	-15.483	-10.070	3.969	1.00	14.23	A
ATOM	566	CG	PHE	A	675	-14.376	-11.054	3.821	1.00	14.93	A
ATOM	567	CD1	PHE	A	675	-13.181	-10.873	4.501	1.00	17.64	A
ATOM	568	CD2	PHE	A	675	-14.543	-12.188	3.040	1.00	16.15	A
ATOM	569	CE1	PHE	A	675	-12.164	-11.815	4.414	1.00	17.02	A
ATOM	570	CE2	PHE	A	675	-13.536	-13.135	2.944	1.00	19.09	A
ATOM	571	CZ	PHE	A	675	-12.342	-12.949	3.636	1.00	18.72	A
ATOM	572	C	PHE	A	675	-14.812	-8.912	1.873	1.00	14.71	A
ATOM	573	O	PHE	A	675	-13.672	-8.655	1.464	1.00	13.96	A
ATOM	574	N	LEU	A	676	-15.780	-9.363	1.080	1.00	13.97	A
ATOM	575	CA	LEU	A	676	-15.550	-9.638	-0.331	1.00	12.30	A
ATOM	576	CB	LEU	A	676	-16.721	-10.465	-0.913	1.00	13.83	A
ATOM	577	CG	LEU	A	676	-16.885	-11.904	-0.364	1.00	13.35	A
ATOM	578	CD1	LEU	A	676	-18.132	-12.553	-0.923	1.00	14.68	A
ATOM	579	CD2	LEU	A	676	-15.665	-12.732	-0.726	1.00	14.56	A
ATOM	580	C	LEU	A	676	-15.318	-8.387	-1.172	1.00	12.89	A
ATOM	581	O	LEU	A	676	-14.816	-8.488	-2.292	1.00	14.97	A
ATOM	582	N	SER	A	677	-15.663	-7.212	-0.651	1.00	11.83	A
ATOM	583	CA	SER	A	677	-15.448	-5.999	-1.438	1.00	14.06	A
ATOM	584	CB	SER	A	677	-16.016	-4.758	-0.733	1.00	12.26	A
ATOM	585	OG	SER	A	677	-15.253	-4.398	0.404	1.00	15.09	A
ATOM	586	C	SER	A	677	-13.952	-5.848	-1.665	1.00	14.36	A
ATOM	587	O	SER	A	677	-13.524	-5.330	-2.685	1.00	14.36	A
ATOM	588	N	GLU	A	678	-13.144	-6.304	-0.715	1.00	16.37	A
ATOM	589	CA	GLU	A	678	-11.705	-6.200	-0.916	1.00	15.57	A
ATOM	590	CB	GLU	A	678	-10.946	-6.832	0.246	1.00	19.69	A

ATOM	591	CG	GLU	A	678	-9.443	-6.939	-0.008	1.00	24.61	A
ATOM	592	CD	GLU	A	678	-8.694	-7.521	1.166	1.00	27.65	A
ATOM	593	OE1	GLU	A	678	-9.219	-8.448	1.807	1.00	29.80	A
ATOM	594	OE2	GLU	A	678	-7.571	-7.052	1.440	1.00	32.17	A
ATOM	595	C	GLU	A	678	-11.328	-6.885	-2.240	1.00	14.92	A
ATOM	596	O	GLU	A	678	-10.498	-6.386	-2.996	1.00	16.05	A
ATOM	597	N	ALA	A	679	-11.958	-8.015	-2.532	1.00	12.66	A
ATOM	598	CA	ALA	A	679	-11.659	-8.737	-3.761	1.00	13.34	A
ATOM	599	CB	ALA	A	679	-12.111	-10.186	-3.650	1.00	9.98	A
ATOM	600	C	ALA	A	679	-12.296	-8.084	-4.981	1.00	13.80	A
ATOM	601	O	ALA	A	679	-11.699	-8.078	-6.059	1.00	12.31	A
ATOM	602	N	SER	A	680	-13.503	-7.544	-4.829	1.00	14.31	A
ATOM	603	CA	SER	A	680	-14.156	-6.915	-5.975	1.00	14.70	A
ATOM	604	CB	SER	A	680	-15.637	-6.606	-5.666	1.00	13.71	A
ATOM	605	OG	SER	A	680	-15.802	-5.683	-4.610	1.00	19.60	A
ATOM	606	C	SER	A	680	-13.369	-5.665	-6.365	1.00	15.81	A
ATOM	607	O	SER	A	680	-13.449	-5.192	-7.496	1.00	17.05	A
ATOM	608	N	ILE	A	681	-12.566	-5.160	-5.431	1.00	15.14	A
ATOM	609	CA	ILE	A	681	-11.739	-3.998	-5.695	1.00	14.43	A
ATOM	610	CB	ILE	A	681	-11.583	-3.167	-4.412	1.00	15.35	A
ATOM	611	CG2	ILE	A	681	-10.483	-2.107	-4.589	1.00	13.45	A
ATOM	612	CG1	ILE	A	681	-12.955	-2.582	-4.050	1.00	12.39	A
ATOM	613	CD1	ILE	A	681	-12.965	-1.725	-2.820	1.00	13.10	A
ATOM	614	C	ILE	A	681	-10.382	-4.441	-6.241	1.00	15.72	A
ATOM	615	O	ILE	A	681	-10.014	-4.091	-7.371	1.00	15.31	A
ATOM	616	N	MET	A	682	-9.658	-5.247	-5.465	1.00	14.71	A
ATOM	617	CA	MET	A	682	-8.349	-5.746	-5.871	1.00	14.74	A
ATOM	618	CB	MET	A	682	-7.862	-6.775	-4.835	1.00	15.19	A
ATOM	619	CG	MET	A	682	-6.417	-7.225	-5.012	1.00	17.99	A
ATOM	620	SD	MET	A	682	-5.958	-8.505	-3.763	1.00	18.16	A
ATOM	621	CE	MET	A	682	-6.407	-7.626	-2.305	1.00	8.10	A
ATOM	622	C	MET	A	682	-8.384	-6.381	-7.267	1.00	13.42	A
ATOM	623	O	MET	A	682	-7.472	-6.179	-8.076	1.00	12.39	A
ATOM	624	N	GLY	A	683	-9.463	-7.108	-7.563	1.00	11.77	A
ATOM	625	CA	GLY	A	683	-9.598	-7.780	-8.856	1.00	10.35	A
ATOM	626	C	GLY	A	683	-9.632	-6.903	-10.105	1.00	11.65	A
ATOM	627	O	GLY	A	683	-9.492	-7.388	-11.229	1.00	10.47	A
ATOM	628	N	GLN	A	684	-9.816	-5.607	-9.911	1.00	11.57	A
ATOM	629	CA	GLN	A	684	-9.862	-4.670	-11.032	1.00	13.82	A
ATOM	630	CB	GLN	A	684	-10.759	-3.487	-10.680	1.00	14.52	A
ATOM	631	CG	GLN	A	684	-12.201	-3.851	-10.377	1.00	13.27	A
ATOM	632	CD	GLN	A	684	-13.003	-2.641	-9.965	1.00	13.03	A
ATOM	633	OE1	GLN	A	684	-12.961	-1.601	-10.637	1.00	14.53	A
ATOM	634	NE2	GLN	A	684	-13.730	-2.754	-8.857	1.00	9.41	A
ATOM	635	C	GLN	A	684	-8.475	-4.129	-11.345	1.00	14.70	A
ATOM	636	O	GLN	A	684	-8.274	-3.438	-12.347	1.00	13.46	A
ATOM	637	N	PHE	A	685	-7.521	-4.425	-10.469	1.00	14.39	A
ATOM	638	CA	PHE	A	685	-6.156	-3.925	-10.639	1.00	14.62	A
ATOM	639	CB	PHE	A	685	-5.644	-3.368	-9.313	1.00	13.37	A
ATOM	640	CG	PHE	A	685	-6.545	-2.344	-8.696	1.00	13.64	A
ATOM	641	CD1	PHE	A	685	-6.742	-2.327	-7.318	1.00	10.36	A
ATOM	642	CD2	PHE	A	685	-7.187	-1.385	-9.483	1.00	12.29	A
ATOM	643	CE1	PHE	A	685	-7.573	-1.361	-6.724	1.00	12.32	A
ATOM	644	CE2	PHE	A	685	-8.016	-0.419	-8.899	1.00	11.59	A
ATOM	645	CZ	PHE	A	685	-8.210	-0.406	-7.520	1.00	13.91	A
ATOM	646	C	PHE	A	685	-5.187	-4.968	-11.146	1.00	14.76	A
ATOM	647	O	PHE	A	685	-5.306	-6.144	-10.836	1.00	15.69	A
ATOM	648	N	ASP	A	686	-4.231	-4.531	-11.952	1.00	15.75	A
ATOM	649	CA	ASP	A	686	-3.230	-5.441	-12.477	1.00	16.52	A
ATOM	650	CB	ASP	A	686	-3.648	-6.006	-13.833	1.00	17.91	A
ATOM	651	CG	ASP	A	686	-2.696	-7.075	-14.319	1.00	20.72	A
ATOM	652	OD1	ASP	A	686	-2.813	-7.517	-15.481	1.00	22.99	A
ATOM	653	OD2	ASP	A	686	-1.820	-7.480	-13.526	1.00	21.44	A
ATOM	654	C	ASP	A	686	-1.929	-4.668	-12.626	1.00	16.22	A

ATOM	655	O	ASP	A	686	-1.645	-4.100	-13.681	1.00	13.75	A
ATOM	656	N	HIS	A	687	-1.143	-4.636	-11.557	1.00	15.08	A
ATOM	657	CA	HIS	A	687	0.114	-3.912	-11.585	1.00	14.22	A
ATOM	658	CB	HIS	A	687	-0.119	-2.460	-11.160	1.00	13.14	A
ATOM	659	CG	HIS	A	687	1.084	-1.585	-11.315	1.00	16.93	A
ATOM	660	CD2	HIS	A	687	1.406	-0.672	-12.264	1.00	15.49	A
ATOM	661	ND1	HIS	A	687	2.141	-1.610	-10.431	1.00	15.21	A
ATOM	662	CE1	HIS	A	687	3.062	-0.748	-10.828	1.00	17.79	A
ATOM	663	NE2	HIS	A	687	2.639	-0.166	-11.937	1.00	16.56	A
ATOM	664	C	HIS	A	687	1.120	-4.598	-10.671	1.00	14.95	A
ATOM	665	O	HIS	A	687	0.766	-5.125	-9.617	1.00	13.04	A
ATOM	666	N	PRO	A	688	2.394	-4.612	-11.076	1.00	15.37	A
ATOM	667	CD	PRO	A	688	2.933	-4.106	-12.355	1.00	13.76	A
ATOM	668	CA	PRO	A	688	3.441	-5.250	-10.275	1.00	14.14	A
ATOM	669	CB	PRO	A	688	4.716	-4.909	-11.048	1.00	16.35	A
ATOM	670	CG	PRO	A	688	4.244	-4.857	-12.483	1.00	16.48	A
ATOM	671	C	PRO	A	688	3.496	-4.785	-8.816	1.00	14.10	A
ATOM	672	O	PRO	A	688	3.868	-5.558	-7.936	1.00	15.51	A
ATOM	673	N	ASN	A	689	3.107	-3.543	-8.545	1.00	12.52	A
ATOM	674	CA	ASN	A	689	3.171	-3.048	-7.173	1.00	12.26	A
ATOM	675	CB	ASN	A	689	3.949	-1.741	-7.144	1.00	11.33	A
ATOM	676	CG	ASN	A	689	5.370	-1.919	-7.629	1.00	13.08	A
ATOM	677	OD1	ASN	A	689	6.237	-2.433	-6.907	1.00	14.93	A
ATOM	678	ND2	ASN	A	689	5.618	-1.524	-8.864	1.00	10.50	A
ATOM	679	C	ASN	A	689	1.840	-2.910	-6.458	1.00	9.30	A
ATOM	680	O	ASN	A	689	1.685	-2.116	-5.543	1.00	9.38	A
ATOM	681	N	VAL	A	690	0.872	-3.696	-6.901	1.00	10.15	A
ATOM	682	CA	VAL	A	690	-0.438	-3.738	-6.275	1.00	10.17	A
ATOM	683	CB	VAL	A	690	-1.523	-3.159	-7.189	1.00	11.34	A
ATOM	684	CG1	VAL	A	690	-2.907	-3.458	-6.593	1.00	5.73	A
ATOM	685	CG2	VAL	A	690	-1.320	-1.643	-7.296	1.00	8.17	A
ATOM	686	C	VAL	A	690	-0.655	-5.232	-6.053	1.00	10.12	A
ATOM	687	O	VAL	A	690	-0.445	-6.038	-6.959	1.00	10.79	A
ATOM	688	N	ILE	A	691	-1.030	-5.601	-4.835	1.00	12.68	A
ATOM	689	CA	ILE	A	691	-1.225	-7.005	-4.482	1.00	12.48	A
ATOM	690	CB	ILE	A	691	-1.833	-7.136	-3.061	1.00	15.22	A
ATOM	691	CG2	ILE	A	691	-2.079	-8.597	-2.729	1.00	17.18	A
ATOM	692	CG1	ILE	A	691	-0.876	-6.555	-2.027	1.00	18.01	A
ATOM	693	CD1	ILE	A	691	0.426	-7.349	-1.935	1.00	24.97	A
ATOM	694	C	ILE	A	691	-2.122	-7.724	-5.478	1.00	14.49	A
ATOM	695	O	ILE	A	691	-3.213	-7.256	-5.798	1.00	14.87	A
ATOM	696	N	HIS	A	692	-1.662	-8.877	-5.948	1.00	14.15	A
ATOM	697	CA	HIS	A	692	-2.409	-9.658	-6.922	1.00	14.37	A
ATOM	698	CB	HIS	A	692	-1.444	-10.529	-7.729	1.00	17.27	A
ATOM	699	CG	HIS	A	692	-2.113	-11.404	-8.745	1.00	19.90	A
ATOM	700	CD2	HIS	A	692	-2.301	-12.743	-8.775	1.00	19.49	A
ATOM	701	ND1	HIS	A	692	-2.671	-10.913	-9.909	1.00	21.64	A
ATOM	702	CE1	HIS	A	692	-3.172	-11.914	-10.610	1.00	20.32	A
ATOM	703	NE2	HIS	A	692	-2.961	-13.035	-9.944	1.00	21.85	A
ATOM	704	C	HIS	A	692	-3.472	-10.542	-6.286	1.00	14.88	A
ATOM	705	O	HIS	A	692	-3.212	-11.229	-5.294	1.00	14.72	A
ATOM	706	N	LEU	A	693	-4.673	-10.513	-6.854	1.00	11.54	A
ATOM	707	CA	LEU	A	693	-5.759	-11.355	-6.369	1.00	11.27	A
ATOM	708	CB	LEU	A	693	-7.113	-10.655	-6.518	1.00	11.71	A
ATOM	709	CG	LEU	A	693	-8.362	-11.527	-6.311	1.00	12.06	A
ATOM	710	CD1	LEU	A	693	-8.584	-11.777	-4.808	1.00	13.97	A
ATOM	711	CD2	LEU	A	693	-9.568	-10.827	-6.903	1.00	12.36	A
ATOM	712	C	LEU	A	693	-5.766	-12.629	-7.202	1.00	12.80	A
ATOM	713	O	LEU	A	693	-5.744	-12.569	-8.432	1.00	12.66	A
ATOM	714	N	GLU	A	694	-5.749	-13.784	-6.541	1.00	9.91	A
ATOM	715	CA	GLU	A	694	-5.803	-15.043	-7.275	1.00	12.11	A
ATOM	716	CB	GLU	A	694	-5.190	-16.197	-6.463	1.00	12.53	A
ATOM	717	CG	GLU	A	694	-3.663	-16.209	-6.417	1.00	15.99	A
ATOM	718	CD	GLU	A	694	-3.024	-16.390	-7.786	1.00	19.23	A

ATOM	719	OE1	GLU	A	694	-3.596	-17.118	-8.633	1.00	22.30	A
ATOM	720	OE2	GLU	A	694	-1.939	-15.817	-8.019	1.00	21.66	A
ATOM	721	C	GLU	A	694	-7.284	-15.311	-7.497	1.00	12.27	A
ATOM	722	O	GLU	A	694	-7.706	-15.664	-8.589	1.00	14.65	A
ATOM	723	N	GLY	A	695	-8.072	-15.126	-6.446	1.00	12.00	A
ATOM	724	CA	GLY	A	695	-9.501	-15.363	-6.554	1.00	13.93	A
ATOM	725	C	GLY	A	695	-10.162	-15.460	-5.191	1.00	14.27	A
ATOM	726	O	GLY	A	695	-9.562	-15.139	-4.165	1.00	15.08	A
ATOM	727	N	VAL	A	696	-11.407	-15.914	-5.185	1.00	16.25	A
ATOM	728	CA	VAL	A	696	-12.160	-16.051	-3.959	1.00	18.13	A
ATOM	729	CB	VAL	A	696	-13.213	-14.920	-3.813	1.00	20.10	A
ATOM	730	CG1	VAL	A	696	-12.523	-13.577	-3.711	1.00	18.53	A
ATOM	731	CG2	VAL	A	696	-14.164	-14.947	-5.011	1.00	18.11	A
ATOM	732	C	VAL	A	696	-12.900	-17.385	-3.944	1.00	20.73	A
ATOM	733	O	VAL	A	696	-13.078	-18.040	-4.984	1.00	20.59	A
ATOM	734	N	VAL	A	697	-13.324	-17.776	-2.752	1.00	20.83	A
ATOM	735	CA	VAL	A	697	-14.086	-18.990	-2.564	1.00	22.28	A
ATOM	736	CB	VAL	A	697	-13.365	-19.983	-1.621	1.00	24.02	A
ATOM	737	CG1	VAL	A	697	-14.184	-21.265	-1.499	1.00	22.46	A
ATOM	738	CG2	VAL	A	697	-11.960	-20.284	-2.156	1.00	22.98	A
ATOM	739	C	VAL	A	697	-15.344	-18.486	-1.880	1.00	22.94	A
ATOM	740	O	VAL	A	697	-15.268	-17.994	-0.758	1.00	22.04	A
ATOM	741	N	THR	A	698	-16.484	-18.568	-2.568	1.00	25.19	A
ATOM	742	CA	THR	A	698	-17.751	-18.113	-2.006	1.00	27.59	A
ATOM	743	CB	THR	A	698	-18.298	-16.854	-2.736	1.00	25.83	A
ATOM	744	OG1	THR	A	698	-18.578	-17.176	-4.099	1.00	23.74	A
ATOM	745	CG2	THR	A	698	-17.287	-15.713	-2.687	1.00	24.82	A
ATOM	746	C	THR	A	698	-18.828	-19.193	-2.076	1.00	31.39	A
ATOM	747	O	THR	A	698	-19.826	-19.119	-1.362	1.00	32.32	A
ATOM	748	N	LYS	A	699	-18.634	-20.186	-2.939	1.00	34.91	A
ATOM	749	CA	LYS	A	699	-19.606	-21.265	-3.085	1.00	38.78	A
ATOM	750	CB	LYS	A	699	-19.632	-21.763	-4.533	1.00	39.53	A
ATOM	751	CG	LYS	A	699	-20.129	-20.728	-5.533	1.00	41.69	A
ATOM	752	CD	LYS	A	699	-20.157	-21.281	-6.953	1.00	43.87	A
ATOM	753	CE	LYS	A	699	-20.685	-20.252	-7.943	1.00	44.93	A
ATOM	754	NZ	LYS	A	699	-20.775	-20.824	-9.328	1.00	47.77	A
ATOM	755	C	LYS	A	699	-19.295	-22.422	-2.145	1.00	40.28	A
ATOM	756	O	LYS	A	699	-19.761	-23.544	-2.342	1.00	42.43	A
ATOM	757	N	SER	A	700	-18.505	-22.139	-1.117	1.00	41.32	A
ATOM	758	CA	SER	A	700	-18.129	-23.146	-0.139	1.00	41.46	A
ATOM	759	CB	SER	A	700	-16.927	-23.949	-0.642	1.00	41.67	A
ATOM	760	OG	SER	A	700	-17.243	-24.643	-1.836	1.00	42.85	A
ATOM	761	C	SER	A	700	-17.776	-22.463	1.176	1.00	41.64	A
ATOM	762	O	SER	A	700	-17.550	-21.252	1.215	1.00	41.74	A
ATOM	763	N	THR	A	701	-17.725	-23.250	2.246	1.00	40.19	A
ATOM	764	CA	THR	A	701	-17.400	-22.745	3.575	1.00	40.36	A
ATOM	765	CB	THR	A	701	-18.451	-23.208	4.618	1.00	41.83	A
ATOM	766	OG1	THR	A	701	-19.763	-22.837	4.175	1.00	44.63	A
ATOM	767	CG2	THR	A	701	-18.190	-22.558	5.973	1.00	42.59	A
ATOM	768	C	THR	A	701	-16.024	-23.256	4.011	1.00	38.95	A
ATOM	769	O	THR	A	701	-15.702	-24.434	3.844	1.00	39.42	A
ATOM	770	N	PRO	A	702	-15.185	-22.370	4.565	1.00	37.14	A
ATOM	771	CD	PRO	A	702	-13.936	-22.766	5.239	1.00	37.05	A
ATOM	772	CA	PRO	A	702	-15.465	-20.949	4.792	1.00	34.67	A
ATOM	773	CB	PRO	A	702	-14.551	-20.611	5.955	1.00	35.95	A
ATOM	774	CG	PRO	A	702	-13.338	-21.429	5.630	1.00	36.79	A
ATOM	775	C	PRO	A	702	-15.158	-20.095	3.569	1.00	31.84	A
ATOM	776	O	PRO	A	702	-14.339	-20.469	2.734	1.00	31.01	A
ATOM	777	N	VAL	A	703	-15.831	-18.952	3.472	1.00	30.06	A
ATOM	778	CA	VAL	A	703	-15.620	-18.017	2.372	1.00	26.08	A
ATOM	779	CB	VAL	A	703	-16.592	-16.830	2.475	1.00	27.78	A
ATOM	780	CG1	VAL	A	703	-16.399	-15.886	1.292	1.00	26.07	A
ATOM	781	CG2	VAL	A	703	-18.028	-17.343	2.525	1.00	27.11	A
ATOM	782	C	VAL	A	703	-14.183	-17.510	2.493	1.00	23.65	A

ATOM	783	O	VAL	A	703	-13.727	-17.199	3.591	1.00	22.73	A
ATOM	784	N	MET	A	704	-13.480	-17.422	1.367	1.00	21.87	A
ATOM	785	CA	MET	A	704	-12.091	-16.985	1.371	1.00	19.85	A
ATOM	786	CB	MET	A	704	-11.154	-18.194	1.287	1.00	20.58	A
ATOM	787	CG	MET	A	704	-11.394	-19.298	2.324	1.00	22.83	A
ATOM	788	SD	MET	A	704	-10.199	-20.637	2.110	1.00	25.21	A
ATOM	789	CE	MET	A	704	-11.006	-21.626	0.904	1.00	26.56	A
ATOM	790	C	MET	A	704	-11.702	-16.055	0.226	1.00	18.73	A
ATOM	791	O	MET	A	704	-12.348	-16.027	-0.817	1.00	18.27	A
ATOM	792	N	ILE	A	705	-10.611	-15.327	0.446	1.00	16.10	A
ATOM	793	CA	ILE	A	705	-10.020	-14.433	-0.541	1.00	14.53	A
ATOM	794	CB	ILE	A	705	-10.033	-12.980	-0.079	1.00	14.98	A
ATOM	795	CG2	ILE	A	705	-9.219	-12.088	-1.066	1.00	13.23	A
ATOM	796	CG1	ILE	A	705	-11.473	-12.508	0.019	1.00	13.64	A
ATOM	797	CD1	ILE	A	705	-11.593	-11.116	0.560	1.00	15.61	A
ATOM	798	C	ILE	A	705	-8.588	-14.917	-0.598	1.00	14.95	A
ATOM	799	O	ILE	A	705	-7.921	-14.999	0.437	1.00	16.93	A
ATOM	800	N	ILE	A	706	-8.125	-15.247	-1.797	1.00	14.61	A
ATOM	801	CA	ILE	A	706	-6.776	-15.761	-1.995	1.00	14.22	A
ATOM	802	CB	ILE	A	706	-6.799	-17.054	-2.837	1.00	13.99	A
ATOM	803	CG2	ILE	A	706	-5.448	-17.747	-2.748	1.00	15.86	A
ATOM	804	CG1	ILE	A	706	-7.914	-17.987	-2.353	1.00	16.58	A
ATOM	805	CD1	ILE	A	706	-7.755	-18.443	-0.919	1.00	23.47	A
ATOM	806	C	ILE	A	706	-5.952	-14.726	-2.741	1.00	14.50	A
ATOM	807	O	ILE	A	706	-6.346	-14.300	-3.829	1.00	12.53	A
ATOM	808	N	THR	A	707	-4.806	-14.342	-2.179	1.00	12.32	A
ATOM	809	CA	THR	A	707	-3.930	-13.344	-2.810	1.00	14.46	A
ATOM	810	CB	THR	A	707	-3.926	-12.026	-2.005	1.00	16.58	A
ATOM	811	OG1	THR	A	707	-3.435	-12.288	-0.685	1.00	18.64	A
ATOM	812	CG2	THR	A	707	-5.334	-11.434	-1.895	1.00	15.55	A
ATOM	813	C	THR	A	707	-2.486	-13.847	-2.921	1.00	16.08	A
ATOM	814	O	THR	A	707	-2.153	-14.876	-2.337	1.00	15.13	A
ATOM	815	N	GLU	A	708	-1.631	-13.150	-3.673	1.00	14.63	A
ATOM	816	CA	GLU	A	708	-0.240	-13.603	-3.798	1.00	16.45	A
ATOM	817	CB	GLU	A	708	0.576	-12.730	-4.779	1.00	16.75	A
ATOM	818	CG	GLU	A	708	0.855	-11.308	-4.315	1.00	17.77	A
ATOM	819	CD	GLU	A	708	1.522	-10.440	-5.399	1.00	18.66	A
ATOM	820	OE1	GLU	A	708	0.897	-9.447	-5.806	1.00	17.59	A
ATOM	821	OE2	GLU	A	708	2.670	-10.747	-5.833	1.00	18.27	A
ATOM	822	C	GLU	A	708	0.412	-13.574	-2.428	1.00	15.05	A
ATOM	823	O	GLU	A	708	0.091	-12.730	-1.582	1.00	12.21	A
ATOM	824	N	PHE	A	709	1.319	-14.516	-2.203	1.00	15.72	A
ATOM	825	CA	PHE	A	709	2.001	-14.599	-0.920	1.00	16.73	A
ATOM	826	CB	PHE	A	709	2.486	-16.035	-0.678	1.00	18.37	A
ATOM	827	CG	PHE	A	709	3.127	-16.238	0.661	1.00	20.59	A
ATOM	828	CD1	PHE	A	709	2.423	-15.975	1.829	1.00	21.91	A
ATOM	829	CD2	PHE	A	709	4.433	-16.690	0.756	1.00	23.57	A
ATOM	830	CE1	PHE	A	709	3.011	-16.160	3.074	1.00	24.66	A
ATOM	831	CE2	PHE	A	709	5.031	-16.881	1.997	1.00	23.90	A
ATOM	832	CZ	PHE	A	709	4.315	-16.614	3.160	1.00	25.45	A
ATOM	833	C	PHE	A	709	3.178	-13.630	-0.890	1.00	15.59	A
ATOM	834	O	PHE	A	709	3.928	-13.541	-1.853	1.00	16.82	A
ATOM	835	N	MET	A	710	3.316	-12.906	0.219	1.00	14.56	A
ATOM	836	CA	MET	A	710	4.393	-11.933	0.410	1.00	16.05	A
ATOM	837	CB	MET	A	710	3.793	-10.539	0.610	1.00	15.84	A
ATOM	838	CG	MET	A	710	2.896	-10.105	-0.547	1.00	16.83	A
ATOM	839	SD	MET	A	710	3.759	-9.890	-2.108	1.00	16.56	A
ATOM	840	CE	MET	A	710	4.355	-8.267	-1.864	1.00	17.49	A
ATOM	841	C	MET	A	710	5.198	-12.365	1.642	1.00	15.49	A
ATOM	842	O	MET	A	710	4.828	-12.075	2.774	1.00	13.99	A
ATOM	843	N	GLU	A	711	6.301	-13.065	1.400	1.00	17.57	A
ATOM	844	CA	GLU	A	711	7.130	-13.597	2.478	1.00	20.55	A
ATOM	845	CB	GLU	A	711	8.369	-14.275	1.906	1.00	23.66	A
ATOM	846	CG	GLU	A	711	8.052	-15.543	1.150	1.00	32.78	A

ATOM	847	CD	GLU	A	711	9.241	-16.479	1.065	1.00	35.60	A
ATOM	848	OE1	GLU	A	711	9.088	-17.579	0.478	1.00	37.62	A
ATOM	849	OE2	GLU	A	711	10.319	-16.112	1.589	1.00	36.45	A
ATOM	850	C	GLU	A	711	7.554	-12.624	3.551	1.00	20.06	A
ATOM	851	O	GLU	A	711	7.577	-12.970	4.728	1.00	20.45	A
ATOM	852	N	ASN	A	712	7.879	-11.403	3.165	1.00	16.84	A
ATOM	853	CA	ASN	A	712	8.322	-10.459	4.160	1.00	15.71	A
ATOM	854	CB	ASN	A	712	9.368	-9.544	3.547	1.00	17.27	A
ATOM	855	CG	ASN	A	712	10.627	-10.303	3.222	1.00	17.78	A
ATOM	856	OD1	ASN	A	712	11.034	-11.157	4.005	1.00	16.07	A
ATOM	857	ND2	ASN	A	712	11.236	-10.026	2.081	1.00	18.84	A
ATOM	858	C	ASN	A	712	7.237	-9.685	4.868	1.00	15.77	A
ATOM	859	O	ASN	A	712	7.515	-8.845	5.711	1.00	13.23	A
ATOM	860	N	GLY	A	713	5.991	-9.995	4.537	1.00	16.18	A
ATOM	861	CA	GLY	A	713	4.884	-9.350	5.207	1.00	13.90	A
ATOM	862	C	GLY	A	713	4.785	-7.846	5.109	1.00	14.53	A
ATOM	863	O	GLY	A	713	5.179	-7.237	4.108	1.00	13.01	A
ATOM	864	N	SER	A	714	4.258	-7.252	6.173	1.00	10.95	A
ATOM	865	CA	SER	A	714	4.068	-5.822	6.231	1.00	15.09	A
ATOM	866	CB	SER	A	714	3.195	-5.470	7.424	1.00	16.14	A
ATOM	867	OG	SER	A	714	1.949	-6.125	7.292	1.00	17.72	A
ATOM	868	C	SER	A	714	5.383	-5.075	6.288	1.00	15.86	A
ATOM	869	O	SER	A	714	6.290	-5.427	7.041	1.00	12.51	A
ATOM	870	N	LEU	A	715	5.457	-4.030	5.476	1.00	14.56	A
ATOM	871	CA	LEU	A	715	6.639	-3.206	5.352	1.00	15.61	A
ATOM	872	CB	LEU	A	715	6.399	-2.141	4.284	1.00	12.49	A
ATOM	873	CG	LEU	A	715	7.574	-1.209	4.012	1.00	15.37	A
ATOM	874	CD1	LEU	A	715	8.786	-2.009	3.583	1.00	12.76	A
ATOM	875	CD2	LEU	A	715	7.161	-0.200	2.907	1.00	12.52	A
ATOM	876	C	LEU	A	715	7.102	-2.540	6.637	1.00	14.75	A
ATOM	877	O	LEU	A	715	8.300	-2.500	6.905	1.00	17.56	A
ATOM	878	N	ASP	A	716	6.180	-2.018	7.444	1.00	15.82	A
ATOM	879	CA	ASP	A	716	6.631	-1.369	8.674	1.00	17.28	A
ATOM	880	CB	ASP	A	716	5.462	-0.652	9.389	1.00	16.92	A
ATOM	881	CG	ASP	A	716	4.361	-1.603	9.849	1.00	19.44	A
ATOM	882	OD1	ASP	A	716	3.995	-2.546	9.109	1.00	17.35	A
ATOM	883	OD2	ASP	A	716	3.850	-1.389	10.964	1.00	22.24	A
ATOM	884	C	ASP	A	716	7.317	-2.397	9.587	1.00	17.91	A
ATOM	885	O	ASP	A	716	8.431	-2.169	10.059	1.00	16.46	A
ATOM	886	N	SER	A	717	6.677	-3.542	9.802	1.00	17.08	A
ATOM	887	CA	SER	A	717	7.266	-4.593	10.654	1.00	17.05	A
ATOM	888	CB	SER	A	717	6.283	-5.747	10.807	1.00	18.18	A
ATOM	889	OG	SER	A	717	5.131	-5.296	11.484	1.00	24.48	A
ATOM	890	C	SER	A	717	8.568	-5.136	10.081	1.00	14.71	A
ATOM	891	O	SER	A	717	9.537	-5.363	10.807	1.00	12.74	A
ATOM	892	N	PHE	A	718	8.576	-5.340	8.766	1.00	13.61	A
ATOM	893	CA	PHE	A	718	9.742	-5.854	8.061	1.00	11.92	A
ATOM	894	CB	PHE	A	718	9.456	-5.913	6.566	1.00	12.48	A
ATOM	895	CG	PHE	A	718	10.624	-6.331	5.736	1.00	12.92	A
ATOM	896	CD1	PHE	A	718	11.172	-7.605	5.873	1.00	13.91	A
ATOM	897	CD2	PHE	A	718	11.155	-5.465	4.780	1.00	13.01	A
ATOM	898	CE1	PHE	A	718	12.229	-8.021	5.069	1.00	14.75	A
ATOM	899	CE2	PHE	A	718	12.209	-5.864	3.969	1.00	10.87	A
ATOM	900	CZ	PHE	A	718	12.752	-7.153	4.110	1.00	14.74	A
ATOM	901	C	PHE	A	718	10.947	-4.968	8.294	1.00	12.69	A
ATOM	902	O	PHE	A	718	12.044	-5.456	8.563	1.00	13.46	A
ATOM	903	N	LEU	A	719	10.736	-3.662	8.176	1.00	13.46	A
ATOM	904	CA	LEU	A	719	11.806	-2.698	8.358	1.00	16.37	A
ATOM	905	CB	LEU	A	719	11.357	-1.299	7.923	1.00	14.77	A
ATOM	906	CG	LEU	A	719	11.232	-1.091	6.407	1.00	18.77	A
ATOM	907	CD1	LEU	A	719	10.819	0.339	6.130	1.00	16.45	A
ATOM	908	CD2	LEU	A	719	12.556	-1.395	5.718	1.00	20.57	A
ATOM	909	C	LEU	A	719	12.280	-2.655	9.797	1.00	14.90	A
ATOM	910	O	LEU	A	719	13.465	-2.497	10.052	1.00	14.07	A

ATOM	911	N	ARG	A	720	11.360	-2.792	10.742	1.00	16.00	A
ATOM	912	CA	ARG	A	720	11.776	-2.759	12.137	1.00	16.42	A
ATOM	913	CB	ARG	A	720	10.563	-2.702	13.062	1.00	18.72	A
ATOM	914	CG	ARG	A	720	10.012	-1.296	13.208	1.00	19.57	A
ATOM	915	CD	ARG	A	720	8.967	-1.164	14.300	1.00	22.51	A
ATOM	916	NE	ARG	A	720	7.624	-1.499	13.843	1.00	28.80	A
ATOM	917	CZ	ARG	A	720	7.146	-2.734	13.738	1.00	31.29	A
ATOM	918	NH1	ARG	A	720	7.902	-3.777	14.063	1.00	33.67	A
ATOM	919	NH2	ARG	A	720	5.903	-2.922	13.311	1.00	31.71	A
ATOM	920	C	ARG	A	720	12.662	-3.951	12.463	1.00	17.27	A
ATOM	921	O	ARG	A	720	13.634	-3.826	13.215	1.00	18.44	A
ATOM	922	N	GLN	A	721	12.348	-5.098	11.870	1.00	16.09	A
ATOM	923	CA	GLN	A	721	13.116	-6.313	12.107	1.00	18.82	A
ATOM	924	CB	GLN	A	721	12.287	-7.532	11.709	1.00	20.62	A
ATOM	925	CG	GLN	A	721	10.946	-7.586	12.403	1.00	25.99	A
ATOM	926	CD	GLN	A	721	10.026	-8.623	11.801	1.00	29.22	A
ATOM	927	OE1	GLN	A	721	10.338	-9.231	10.768	1.00	31.08	A
ATOM	928	NE2	GLN	A	721	8.875	-8.827	12.435	1.00	30.60	A
ATOM	929	C	GLN	A	721	14.426	-6.339	11.332	1.00	18.64	A
ATOM	930	O	GLN	A	721	15.242	-7.261	11.481	1.00	17.28	A
ATOM	931	N	ASN	A	722	14.619	-5.326	10.499	1.00	17.52	A
ATOM	932	CA	ASN	A	722	15.813	-5.236	9.676	1.00	17.80	A
ATOM	933	CB	ASN	A	722	15.469	-5.642	8.241	1.00	17.53	A
ATOM	934	CG	ASN	A	722	15.262	-7.143	8.100	1.00	20.53	A
ATOM	935	OD1	ASN	A	722	16.227	-7.901	8.085	1.00	22.10	A
ATOM	936	ND2	ASN	A	722	13.997	-7.582	8.015	1.00	17.67	A
ATOM	937	C	ASN	A	722	16.347	-3.820	9.719	1.00	17.61	A
ATOM	938	O	ASN	A	722	16.752	-3.268	8.697	1.00	18.91	A
ATOM	939	N	ASP	A	723	16.361	-3.247	10.919	1.00	17.15	A
ATOM	940	CA	ASP	A	723	16.817	-1.887	11.101	1.00	19.13	A
ATOM	941	CB	ASP	A	723	16.702	-1.498	12.582	1.00	23.22	A
ATOM	942	CG	ASP	A	723	17.064	-0.043	12.844	1.00	26.94	A
ATOM	943	OD1	ASP	A	723	16.687	0.837	12.049	1.00	28.14	A
ATOM	944	OD2	ASP	A	723	17.728	0.220	13.869	1.00	30.54	A
ATOM	945	C	ASP	A	723	18.244	-1.685	10.569	1.00	19.80	A
ATOM	946	O	ASP	A	723	19.168	-2.433	10.906	1.00	15.82	A
ATOM	947	N	GLY	A	724	18.374	-0.682	9.698	1.00	16.08	A
ATOM	948	CA	GLY	A	724	19.644	-0.327	9.089	1.00	15.30	A
ATOM	949	C	GLY	A	724	20.264	-1.401	8.220	1.00	14.31	A
ATOM	950	O	GLY	A	724	21.430	-1.314	7.855	1.00	13.94	A
ATOM	951	N	GLN	A	725	19.481	-2.402	7.843	1.00	14.27	A
ATOM	952	CA	GLN	A	725	20.030	-3.503	7.064	1.00	14.66	A
ATOM	953	CB	GLN	A	725	19.286	-4.784	7.418	1.00	16.87	A
ATOM	954	CG	GLN	A	725	19.316	-5.104	8.912	1.00	18.98	A
ATOM	955	CD	GLN	A	725	20.744	-5.203	9.445	1.00	20.91	A
ATOM	956	OE1	GLN	A	725	21.198	-4.338	10.202	1.00	25.17	A
ATOM	957	NE2	GLN	A	725	21.456	-6.248	9.044	1.00	18.71	A
ATOM	958	C	GLN	A	725	20.092	-3.349	5.557	1.00	14.70	A
ATOM	959	O	GLN	A	725	20.722	-4.162	4.895	1.00	13.92	A
ATOM	960	N	PHE	A	726	19.454	-2.321	5.011	1.00	13.07	A
ATOM	961	CA	PHE	A	726	19.459	-2.151	3.561	1.00	15.29	A
ATOM	962	CB	PHE	A	726	18.016	-1.995	3.085	1.00	14.57	A
ATOM	963	CG	PHE	A	726	17.140	-3.143	3.477	1.00	15.22	A
ATOM	964	CD1	PHE	A	726	16.094	-2.966	4.375	1.00	14.78	A
ATOM	965	CD2	PHE	A	726	17.399	-4.419	2.984	1.00	14.88	A
ATOM	966	CE1	PHE	A	726	15.325	-4.042	4.776	1.00	13.36	A
ATOM	967	CE2	PHE	A	726	16.630	-5.505	3.386	1.00	17.90	A
ATOM	968	CZ	PHE	A	726	15.594	-5.314	4.285	1.00	14.76	A
ATOM	969	C	PHE	A	726	20.300	-0.997	3.050	1.00	13.71	A
ATOM	970	O	PHE	A	726	20.627	-0.070	3.794	1.00	16.24	A
ATOM	971	N	THR	A	727	20.669	-1.066	1.776	1.00	17.14	A
ATOM	972	CA	THR	A	727	21.443	0.020	1.184	1.00	17.33	A
ATOM	973	CB	THR	A	727	22.177	-0.429	-0.095	1.00	17.31	A
ATOM	974	OG1	THR	A	727	21.233	-0.637	-1.148	1.00	16.76	A

ATOM	975	CG2	THR	A	727	22.934	-1.744	0.153	1.00	17.77	A
ATOM	976	C	THR	A	727	20.438	1.121	0.851	1.00	19.38	A
ATOM	977	O	THR	A	727	19.224	0.881	0.853	1.00	18.71	A
ATOM	978	N	VAL	A	728	20.941	2.326	0.601	1.00	17.57	A
ATOM	979	CA	VAL	A	728	20.090	3.465	0.257	1.00	18.19	A
ATOM	980	CB	VAL	A	728	20.924	4.776	0.134	1.00	19.55	A
ATOM	981	CG1	VAL	A	728	20.029	5.939	-0.320	1.00	20.05	A
ATOM	982	CG2	VAL	A	728	21.550	5.118	1.487	1.00	18.70	A
ATOM	983	C	VAL	A	728	19.367	3.184	-1.066	1.00	16.00	A
ATOM	984	O	VAL	A	728	18.181	3.482	-1.216	1.00	15.83	A
ATOM	985	N	ILE	A	729	20.085	2.603	-2.019	1.00	16.06	A
ATOM	986	CA	ILE	A	729	19.490	2.274	-3.306	1.00	16.24	A
ATOM	987	CB	ILE	A	729	20.565	1.765	-4.297	1.00	15.78	A
ATOM	988	CG2	ILE	A	729	19.949	0.856	-5.350	1.00	14.65	A
ATOM	989	CG1	ILE	A	729	21.272	2.962	-4.948	1.00	18.50	A
ATOM	990	CD1	ILE	A	729	20.387	3.784	-5.889	1.00	16.84	A
ATOM	991	C	ILE	A	729	18.375	1.247	-3.137	1.00	17.15	A
ATOM	992	O	ILE	A	729	17.377	1.274	-3.870	1.00	13.45	A
ATOM	993	N	GLN	A	730	18.521	0.342	-2.172	1.00	16.67	A
ATOM	994	CA	GLN	A	730	17.461	-0.649	-1.962	1.00	16.00	A
ATOM	995	CB	GLN	A	730	17.922	-1.763	-1.015	1.00	16.68	A
ATOM	996	CG	GLN	A	730	18.885	-2.733	-1.646	1.00	15.89	A
ATOM	997	CD	GLN	A	730	19.389	-3.777	-0.661	1.00	16.94	A
ATOM	998	OE1	GLN	A	730	19.843	-3.437	0.441	1.00	15.33	A
ATOM	999	NE2	GLN	A	730	19.312	-5.049	-1.052	1.00	13.76	A
ATOM	1000	C	GLN	A	730	16.202	0.008	-1.397	1.00	15.38	A
ATOM	1001	O	GLN	A	730	15.084	-0.284	-1.838	1.00	15.30	A
ATOM	1002	N	LEU	A	731	16.385	0.896	-0.424	1.00	14.09	A
ATOM	1003	CA	LEU	A	731	15.256	1.589	0.193	1.00	14.64	A
ATOM	1004	CB	LEU	A	731	15.721	2.437	1.377	1.00	13.73	A
ATOM	1005	CG	LEU	A	731	16.298	1.671	2.577	1.00	15.51	A
ATOM	1006	CD1	LEU	A	731	16.848	2.669	3.569	1.00	15.48	A
ATOM	1007	CD2	LEU	A	731	15.227	0.797	3.228	1.00	15.71	A
ATOM	1008	C	LEU	A	731	14.570	2.480	-0.828	1.00	15.58	A
ATOM	1009	O	LEU	A	731	13.341	2.582	-0.851	1.00	13.60	A
ATOM	1010	N	VAL	A	732	15.368	3.137	-1.665	1.00	14.16	A
ATOM	1011	CA	VAL	A	732	14.798	4.003	-2.687	1.00	13.56	A
ATOM	1012	CB	VAL	A	732	15.881	4.746	-3.497	1.00	12.54	A
ATOM	1013	CG1	VAL	A	732	15.225	5.497	-4.664	1.00	13.40	A
ATOM	1014	CG2	VAL	A	732	16.596	5.748	-2.598	1.00	12.18	A
ATOM	1015	C	VAL	A	732	13.980	3.137	-3.636	1.00	12.77	A
ATOM	1016	O	VAL	A	732	12.917	3.548	-4.097	1.00	16.70	A
ATOM	1017	N	GLY	A	733	14.479	1.932	-3.896	1.00	12.87	A
ATOM	1018	CA	GLY	A	733	13.796	1.003	-4.776	1.00	11.87	A
ATOM	1019	C	GLY	A	733	12.438	0.597	-4.231	1.00	12.83	A
ATOM	1020	O	GLY	A	733	11.485	0.367	-4.989	1.00	10.23	A
ATOM	1021	N	MET	A	734	12.347	0.499	-2.908	1.00	11.75	A
ATOM	1022	CA	MET	A	734	11.086	0.146	-2.263	1.00	11.65	A
ATOM	1023	CB	MET	A	734	11.298	-0.137	-0.773	1.00	11.18	A
ATOM	1024	CG	MET	A	734	12.101	-1.393	-0.479	1.00	13.32	A
ATOM	1025	SD	MET	A	734	12.561	-1.491	1.285	1.00	17.57	A
ATOM	1026	CE	MET	A	734	13.565	-2.978	1.245	1.00	14.96	A
ATOM	1027	C	MET	A	734	10.096	1.297	-2.419	1.00	12.17	A
ATOM	1028	O	MET	A	734	8.916	1.093	-2.732	1.00	12.13	A
ATOM	1029	N	LEU	A	735	10.590	2.510	-2.211	1.00	10.98	A
ATOM	1030	CA	LEU	A	735	9.751	3.692	-2.312	1.00	12.80	A
ATOM	1031	CB	LEU	A	735	10.509	4.919	-1.789	1.00	13.81	A
ATOM	1032	CG	LEU	A	735	10.854	4.931	-0.283	1.00	14.22	A
ATOM	1033	CD1	LEU	A	735	11.767	6.115	0.009	1.00	15.97	A
ATOM	1034	CD2	LEU	A	735	9.592	5.036	0.554	1.00	14.12	A
ATOM	1035	C	LEU	A	735	9.277	3.909	-3.756	1.00	12.46	A
ATOM	1036	O	LEU	A	735	8.162	4.387	-3.991	1.00	12.21	A
ATOM	1037	N	ARG	A	736	10.126	3.535	-4.707	1.00	11.75	A
ATOM	1038	CA	ARG	A	736	9.822	3.640	-6.141	1.00	13.68	A

ATOM	1039	CB	ARG	A	736	11.061	3.264	-6.961	1.00	15.62	A
ATOM	1040	CG	ARG	A	736	10.798	2.724	-8.368	1.00	22.11	A
ATOM	1041	CD	ARG	A	736	10.163	3.773	-9.223	1.00	21.46	A
ATOM	1042	NE	ARG	A	736	10.472	3.653	-10.651	1.00	25.32	A
ATOM	1043	CZ	ARG	A	736	9.737	3.010	-11.560	1.00	26.66	A
ATOM	1044	NH1	ARG	A	736	8.621	2.386	-11.212	1.00	27.03	A
ATOM	1045	NH2	ARG	A	736	10.092	3.040	-12.848	1.00	26.16	A
ATOM	1046	C	ARG	A	736	8.674	2.697	-6.484	1.00	14.97	A
ATOM	1047	O	ARG	A	736	7.713	3.078	-7.155	1.00	14.53	A
ATOM	1048	N	GLY	A	737	8.788	1.462	-6.010	1.00	14.21	A
ATOM	1049	CA	GLY	A	737	7.757	0.474	-6.256	1.00	13.57	A
ATOM	1050	C	GLY	A	737	6.422	0.906	-5.684	1.00	12.80	A
ATOM	1051	O	GLY	A	737	5.390	0.716	-6.314	1.00	11.94	A
ATOM	1052	N	ILE	A	738	6.437	1.492	-4.490	1.00	14.09	A
ATOM	1053	CA	ILE	A	738	5.208	1.943	-3.855	1.00	11.56	A
ATOM	1054	CB	ILE	A	738	5.467	2.392	-2.405	1.00	11.50	A
ATOM	1055	CG2	ILE	A	738	4.195	3.031	-1.825	1.00	9.80	A
ATOM	1056	CG1	ILE	A	738	5.917	1.175	-1.558	1.00	8.91	A
ATOM	1057	CD1	ILE	A	738	6.389	1.544	-0.153	1.00	8.26	A
ATOM	1058	C	ILE	A	738	4.584	3.110	-4.640	1.00	13.67	A
ATOM	1059	O	ILE	A	738	3.374	3.141	-4.871	1.00	11.58	A
ATOM	1060	N	ALA	A	739	5.416	4.055	-5.070	1.00	12.15	A
ATOM	1061	CA	ALA	A	739	4.918	5.207	-5.831	1.00	12.85	A
ATOM	1062	CB	ALA	A	739	6.054	6.219	-6.067	1.00	9.40	A
ATOM	1063	C	ALA	A	739	4.354	4.728	-7.170	1.00	10.80	A
ATOM	1064	O	ALA	A	739	3.374	5.277	-7.679	1.00	13.80	A
ATOM	1065	N	ALA	A	740	4.980	3.708	-7.736	1.00	8.81	A
ATOM	1066	CA	ALA	A	740	4.526	3.169	-9.009	1.00	11.12	A
ATOM	1067	CB	ALA	A	740	5.508	2.129	-9.514	1.00	9.71	A
ATOM	1068	C	ALA	A	740	3.151	2.532	-8.830	1.00	12.53	A
ATOM	1069	O	ALA	A	740	2.262	2.721	-9.655	1.00	9.41	A
ATOM	1070	N	GLY	A	741	2.992	1.748	-7.765	1.00	10.66	A
ATOM	1071	CA	GLY	A	741	1.700	1.138	-7.516	1.00	10.59	A
ATOM	1072	C	GLY	A	741	0.642	2.211	-7.310	1.00	10.74	A
ATOM	1073	O	GLY	A	741	-0.460	2.097	-7.838	1.00	11.88	A
ATOM	1074	N	MET	A	742	0.988	3.260	-6.564	1.00	9.32	A
ATOM	1075	CA	MET	A	742	0.057	4.342	-6.278	1.00	10.60	A
ATOM	1076	CB	MET	A	742	0.593	5.246	-5.170	1.00	9.60	A
ATOM	1077	CG	MET	A	742	0.530	4.658	-3.753	1.00	15.00	A
ATOM	1078	SD	MET	A	742	-1.113	4.092	-3.272	1.00	12.37	A
ATOM	1079	CE	MET	A	742	-1.973	5.605	-3.201	1.00	7.46	A
ATOM	1080	C	MET	A	742	-0.274	5.184	-7.506	1.00	11.90	A
ATOM	1081	O	MET	A	742	-1.396	5.681	-7.636	1.00	11.73	A
ATOM	1082	N	LYS	A	743	0.710	5.362	-8.382	1.00	12.27	A
ATOM	1083	CA	LYS	A	743	0.510	6.128	-9.606	1.00	14.85	A
ATOM	1084	CB	LYS	A	743	1.828	6.206	-10.386	1.00	14.51	A
ATOM	1085	CG	LYS	A	743	1.892	7.305	-11.431	1.00	17.54	A
ATOM	1086	CD	LYS	A	743	1.282	6.871	-12.720	1.00	18.67	A
ATOM	1087	CE	LYS	A	743	1.404	7.987	-13.780	1.00	21.38	A
ATOM	1088	NZ	LYS	A	743	0.863	7.526	-15.088	1.00	19.61	A
ATOM	1089	C	LYS	A	743	-0.554	5.375	-10.406	1.00	14.04	A
ATOM	1090	O	LYS	A	743	-1.503	5.971	-10.918	1.00	15.53	A
ATOM	1091	N	TYR	A	744	-0.401	4.055	-10.474	1.00	11.88	A
ATOM	1092	CA	TYR	A	744	-1.341	3.213	-11.194	1.00	11.73	A
ATOM	1093	CB	TYR	A	744	-0.884	1.747	-11.168	1.00	10.89	A
ATOM	1094	CG	TYR	A	744	-1.920	0.774	-11.699	1.00	12.71	A
ATOM	1095	CD1	TYR	A	744	-2.013	0.478	-13.063	1.00	11.56	A
ATOM	1096	CE1	TYR	A	744	-2.969	-0.441	-13.543	1.00	12.70	A
ATOM	1097	CD2	TYR	A	744	-2.807	0.144	-10.832	1.00	11.18	A
ATOM	1098	CE2	TYR	A	744	-3.756	-0.760	-11.299	1.00	12.54	A
ATOM	1099	CZ	TYR	A	744	-3.830	-1.054	-12.644	1.00	12.73	A
ATOM	1100	OH	TYR	A	744	-4.728	-2.010	-13.051	1.00	13.10	A
ATOM	1101	C	TYR	A	744	-2.761	3.333	-10.600	1.00	13.06	A
ATOM	1102	O	TYR	A	744	-3.725	3.511	-11.339	1.00	12.71	A

ATOM	1103	N	LEU	A	745	-2.892	3.239	-9.273	1.00	11.93	A
ATOM	1104	CA	LEU	A	745	-4.203	3.364	-8.634	1.00	9.55	A
ATOM	1105	CB	LEU	A	745	-4.098	3.129	-7.117	1.00	12.28	A
ATOM	1106	CG	LEU	A	745	-3.548	1.739	-6.716	1.00	10.40	A
ATOM	1107	CD1	LEU	A	745	-3.313	1.648	-5.206	1.00	11.47	A
ATOM	1108	CD2	LEU	A	745	-4.550	0.682	-7.149	1.00	13.02	A
ATOM	1109	C	LEU	A	745	-4.808	4.755	-8.898	1.00	12.15	A
ATOM	1110	O	LEU	A	745	-5.991	4.876	-9.231	1.00	11.72	A
ATOM	1111	N	ALA	A	746	-4.000	5.796	-8.732	1.00	13.75	A
ATOM	1112	CA	ALA	A	746	-4.447	7.159	-8.972	1.00	13.62	A
ATOM	1113	CB	ALA	A	746	-3.289	8.153	-8.704	1.00	14.55	A
ATOM	1114	C	ALA	A	746	-4.930	7.270	-10.425	1.00	14.12	A
ATOM	1115	O	ALA	A	746	-5.965	7.877	-10.694	1.00	16.20	A
ATOM	1116	N	ASP	A	747	-4.194	6.668	-11.356	1.00	13.55	A
ATOM	1117	CA	ASP	A	747	-4.583	6.692	-12.773	1.00	14.00	A
ATOM	1118	CB	ASP	A	747	-3.563	5.961	-13.641	1.00	14.56	A
ATOM	1119	CG	ASP	A	747	-2.358	6.820	-14.001	1.00	10.40	A
ATOM	1120	OD1	ASP	A	747	-2.345	8.018	-13.679	1.00	11.42	A
ATOM	1121	OD2	ASP	A	747	-1.438	6.263	-14.625	1.00	13.31	A
ATOM	1122	C	ASP	A	747	-5.939	6.023	-12.995	1.00	17.40	A
ATOM	1123	O	ASP	A	747	-6.680	6.391	-13.921	1.00	13.00	A
ATOM	1124	N	MET	A	748	-6.238	5.032	-12.151	1.00	15.80	A
ATOM	1125	CA	MET	A	748	-7.491	4.263	-12.210	1.00	17.56	A
ATOM	1126	CB	MET	A	748	-7.333	2.914	-11.491	1.00	18.98	A
ATOM	1127	CG	MET	A	748	-6.414	1.918	-12.149	1.00	24.30	A
ATOM	1128	SD	MET	A	748	-7.172	1.067	-13.532	1.00	32.75	A
ATOM	1129	CE	MET	A	748	-8.491	0.141	-12.704	1.00	26.32	A
ATOM	1130	C	MET	A	748	-8.593	5.022	-11.493	1.00	16.57	A
ATOM	1131	O	MET	A	748	-9.744	4.557	-11.402	1.00	17.25	A
ATOM	1132	N	ASN	A	749	-8.223	6.175	-10.954	1.00	15.84	A
ATOM	1133	CA	ASN	A	749	-9.148	7.007	-10.198	1.00	17.28	A
ATOM	1134	CB	ASN	A	749	-10.408	7.295	-11.017	1.00	22.09	A
ATOM	1135	CG	ASN	A	749	-11.210	8.431	-10.447	1.00	25.81	A
ATOM	1136	OD1	ASN	A	749	-10.647	9.371	-9.892	1.00	29.95	A
ATOM	1137	ND2	ASN	A	749	-12.528	8.363	-10.580	1.00	31.13	A
ATOM	1138	C	ASN	A	749	-9.528	6.329	-8.875	1.00	16.80	A
ATOM	1139	O	ASN	A	749	-10.660	6.444	-8.388	1.00	14.69	A
ATOM	1140	N	TYR	A	750	-8.579	5.608	-8.293	1.00	16.08	A
ATOM	1141	CA	TYR	A	750	-8.827	4.949	-7.007	1.00	13.01	A
ATOM	1142	CB	TYR	A	750	-8.345	3.498	-7.042	1.00	13.41	A
ATOM	1143	CG	TYR	A	750	-8.556	2.791	-5.721	1.00	13.96	A
ATOM	1144	CD1	TYR	A	750	-9.792	2.249	-5.402	1.00	11.49	A
ATOM	1145	CE1	TYR	A	750	-10.022	1.633	-4.175	1.00	13.84	A
ATOM	1146	CD2	TYR	A	750	-7.530	2.704	-4.774	1.00	13.22	A
ATOM	1147	CE2	TYR	A	750	-7.749	2.088	-3.534	1.00	13.77	A
ATOM	1148	CZ	TYR	A	750	-9.003	1.559	-3.251	1.00	14.92	A
ATOM	1149	OH	TYR	A	750	-9.262	0.963	-2.028	1.00	15.35	A
ATOM	1150	C	TYR	A	750	-8.039	5.699	-5.934	1.00	13.00	A
ATOM	1151	O	TYR	A	750	-6.814	5.785	-6.012	1.00	13.01	A
ATOM	1152	N	VAL	A	751	-8.743	6.256	-4.955	1.00	14.41	A
ATOM	1153	CA	VAL	A	751	-8.111	6.968	-3.843	1.00	15.71	A
ATOM	1154	CB	VAL	A	751	-8.968	8.151	-3.365	1.00	17.55	A
ATOM	1155	CG1	VAL	A	751	-8.324	8.792	-2.143	1.00	20.77	A
ATOM	1156	CG2	VAL	A	751	-9.123	9.181	-4.491	1.00	18.56	A
ATOM	1157	C	VAL	A	751	-8.027	5.946	-2.715	1.00	16.81	A
ATOM	1158	O	VAL	A	751	-9.058	5.449	-2.267	1.00	15.55	A
ATOM	1159	N	HIS	A	752	-6.814	5.643	-2.258	1.00	14.86	A
ATOM	1160	CA	HIS	A	752	-6.612	4.645	-1.209	1.00	13.56	A
ATOM	1161	CB	HIS	A	752	-5.123	4.316	-1.085	1.00	11.05	A
ATOM	1162	CG	HIS	A	752	-4.852	3.078	-0.290	1.00	8.71	A
ATOM	1163	CD2	HIS	A	752	-4.529	1.825	-0.681	1.00	10.79	A
ATOM	1164	ND1	HIS	A	752	-4.946	3.039	1.084	1.00	10.98	A
ATOM	1165	CE1	HIS	A	752	-4.688	1.814	1.505	1.00	11.77	A
ATOM	1166	NE2	HIS	A	752	-4.431	1.060	0.454	1.00	10.75	A

ATOM	1167	C	HIS	A	752	-7.149	5.044	0.161	1.00	14.58	A
ATOM	1168	O	HIS	A	752	-7.821	4.251	0.830	1.00	16.10	A
ATOM	1169	N	ARG	A	753	-6.825	6.269	0.573	1.00	15.29	A
ATOM	1170	CA	ARG	A	753	-7.251	6.827	1.855	1.00	17.04	A
ATOM	1171	CB	ARG	A	753	-8.755	6.598	2.068	1.00	21.60	A
ATOM	1172	CG	ARG	A	753	-9.654	7.287	1.056	1.00	25.77	A
ATOM	1173	CD	ARG	A	753	-11.110	7.212	1.484	1.00	31.38	A
ATOM	1174	NE	ARG	A	753	-11.969	8.087	0.685	1.00	33.80	A
ATOM	1175	CZ	ARG	A	753	-13.158	8.533	1.082	1.00	36.41	A
ATOM	1176	NH1	ARG	A	753	-13.637	8.187	2.271	1.00	35.80	A
ATOM	1177	NH2	ARG	A	753	-13.864	9.336	0.295	1.00	37.87	A
ATOM	1178	C	ARG	A	753	-6.503	6.326	3.097	1.00	16.08	A
ATOM	1179	O	ARG	A	753	-6.555	6.972	4.144	1.00	15.20	A
ATOM	1180	N	ASP	A	754	-5.819	5.189	3.008	1.00	14.97	A
ATOM	1181	CA	ASP	A	754	-5.101	4.667	4.180	1.00	16.09	A
ATOM	1182	CB	ASP	A	754	-5.941	3.555	4.826	1.00	18.24	A
ATOM	1183	CG	ASP	A	754	-5.413	3.098	6.188	1.00	23.23	A
ATOM	1184	OD1	ASP	A	754	-4.927	3.920	6.990	1.00	25.55	A
ATOM	1185	OD2	ASP	A	754	-5.515	1.881	6.469	1.00	28.99	A
ATOM	1186	C	ASP	A	754	-3.702	4.161	3.796	1.00	14.92	A
ATOM	1187	O	ASP	A	754	-3.280	3.078	4.201	1.00	13.06	A
ATOM	1188	N	LEU	A	755	-2.993	4.955	2.998	1.00	14.02	A
ATOM	1189	CA	LEU	A	755	-1.652	4.594	2.572	1.00	13.51	A
ATOM	1190	CB	LEU	A	755	-1.212	5.454	1.384	1.00	9.06	A
ATOM	1191	CG	LEU	A	755	0.216	5.254	0.884	1.00	10.93	A
ATOM	1192	CD1	LEU	A	755	0.452	3.797	0.483	1.00	9.97	A
ATOM	1193	CD2	LEU	A	755	0.458	6.186	-0.312	1.00	8.65	A
ATOM	1194	C	LEU	A	755	-0.705	4.772	3.758	1.00	13.01	A
ATOM	1195	O	LEU	A	755	-0.596	5.859	4.346	1.00	13.78	A
ATOM	1196	N	ALA	A	756	-0.043	3.675	4.110	1.00	12.68	A
ATOM	1197	CA	ALA	A	756	0.876	3.623	5.247	1.00	11.51	A
ATOM	1198	CB	ALA	A	756	0.068	3.568	6.560	1.00	9.75	A
ATOM	1199	C	ALA	A	756	1.732	2.361	5.094	1.00	10.18	A
ATOM	1200	O	ALA	A	756	1.303	1.398	4.465	1.00	7.97	A
ATOM	1201	N	ALA	A	757	2.930	2.346	5.671	1.00	7.85	A
ATOM	1202	CA	ALA	A	757	3.802	1.186	5.514	1.00	8.61	A
ATOM	1203	CB	ALA	A	757	5.153	1.430	6.239	1.00	7.83	A
ATOM	1204	C	ALA	A	757	3.148	-0.117	6.016	1.00	8.24	A
ATOM	1205	O	ALA	A	757	3.423	-1.189	5.490	1.00	10.34	A
ATOM	1206	N	ARG	A	758	2.279	-0.026	7.016	1.00	10.60	A
ATOM	1207	CA	ARG	A	758	1.607	-1.219	7.537	1.00	12.89	A
ATOM	1208	CB	ARG	A	758	0.806	-0.895	8.809	1.00	14.94	A
ATOM	1209	CG	ARG	A	758	-0.235	0.190	8.616	1.00	20.57	A
ATOM	1210	CD	ARG	A	758	-1.226	0.256	9.775	1.00	23.51	A
ATOM	1211	NE	ARG	A	758	-2.251	1.267	9.517	1.00	26.29	A
ATOM	1212	CZ	ARG	A	758	-2.017	2.574	9.514	1.00	26.89	A
ATOM	1213	NH1	ARG	A	758	-0.794	3.029	9.762	1.00	28.84	A
ATOM	1214	NH2	ARG	A	758	-2.999	3.425	9.259	1.00	29.97	A
ATOM	1215	C	ARG	A	758	0.667	-1.782	6.479	1.00	13.53	A
ATOM	1216	O	ARG	A	758	0.245	-2.942	6.555	1.00	11.71	A
ATOM	1217	N	ASN	A	759	0.348	-0.960	5.486	1.00	12.82	A
ATOM	1218	CA	ASN	A	759	-0.542	-1.401	4.421	1.00	14.76	A
ATOM	1219	CB	ASN	A	759	-1.659	-0.368	4.217	1.00	13.84	A
ATOM	1220	CG	ASN	A	759	-2.575	-0.315	5.409	1.00	17.87	A
ATOM	1221	OD1	ASN	A	759	-2.929	-1.366	5.947	1.00	14.41	A
ATOM	1222	ND2	ASN	A	759	-2.942	0.888	5.853	1.00	16.21	A
ATOM	1223	C	ASN	A	759	0.175	-1.727	3.117	1.00	14.12	A
ATOM	1224	O	ASN	A	759	-0.450	-1.885	2.067	1.00	16.83	A
ATOM	1225	N	ILE	A	760	1.499	-1.823	3.194	1.00	12.17	A
ATOM	1226	CA	ILE	A	760	2.316	-2.195	2.045	1.00	10.80	A
ATOM	1227	CB	ILE	A	760	3.503	-1.198	1.811	1.00	10.66	A
ATOM	1228	CG2	ILE	A	760	4.335	-1.671	0.629	1.00	7.31	A
ATOM	1229	CG1	ILE	A	760	2.992	0.233	1.571	1.00	9.62	A
ATOM	1230	CD1	ILE	A	760	2.035	0.369	0.357	1.00	10.93	A

ATOM	1231	C	ILE	A	760	2.905	-3.587	2.374	1.00	12.66	A
ATOM	1232	O	ILE	A	760	3.390	-3.801	3.496	1.00	14.01	A
ATOM	1233	N	LEU	A	761	2.846	-4.534	1.431	1.00	10.97	A
ATOM	1234	CA	LEU	A	761	3.409	-5.874	1.673	1.00	13.49	A
ATOM	1235	CB	LEU	A	761	2.452	-6.983	1.222	1.00	12.03	A
ATOM	1236	CG	LEU	A	761	1.135	-7.005	1.998	1.00	15.46	A
ATOM	1237	CD1	LEU	A	761	0.168	-8.010	1.371	1.00	15.87	A
ATOM	1238	CD2	LEU	A	761	1.418	-7.372	3.443	1.00	20.01	A
ATOM	1239	C	LEU	A	761	4.741	-6.004	0.936	1.00	12.83	A
ATOM	1240	O	LEU	A	761	4.955	-5.356	-0.085	1.00	11.29	A
ATOM	1241	N	VAL	A	762	5.623	-6.853	1.457	1.00	11.95	A
ATOM	1242	CA	VAL	A	762	6.957	-7.030	0.885	1.00	10.52	A
ATOM	1243	CB	VAL	A	762	8.017	-6.525	1.894	1.00	11.59	A
ATOM	1244	CG1	VAL	A	762	9.400	-6.502	1.267	1.00	10.27	A
ATOM	1245	CG2	VAL	A	762	7.627	-5.142	2.388	1.00	11.18	A
ATOM	1246	C	VAL	A	762	7.243	-8.488	0.525	1.00	11.69	A
ATOM	1247	O	VAL	A	762	7.014	-9.390	1.341	1.00	11.49	A
ATOM	1248	N	ASN	A	763	7.740	-8.734	-0.688	1.00	10.00	A
ATOM	1249	CA	ASN	A	763	8.028	-10.105	-1.082	1.00	13.20	A
ATOM	1250	CB	ASN	A	763	7.586	-10.369	-2.543	1.00	14.49	A
ATOM	1251	CG	ASN	A	763	8.550	-9.829	-3.587	1.00	15.38	A
ATOM	1252	OD1	ASN	A	763	9.605	-9.278	-3.274	1.00	17.52	A
ATOM	1253	ND2	ASN	A	763	8.186	-10.010	-4.855	1.00	17.84	A
ATOM	1254	C	ASN	A	763	9.487	-10.470	-0.842	1.00	14.94	A
ATOM	1255	O	ASN	A	763	10.259	-9.643	-0.358	1.00	15.44	A
ATOM	1256	N	SER	A	764	9.862	-11.711	-1.142	1.00	17.21	A
ATOM	1257	CA	SER	A	764	11.233	-12.153	-0.897	1.00	19.91	A
ATOM	1258	CB	SER	A	764	11.372	-13.649	-1.186	1.00	20.57	A
ATOM	1259	OG	SER	A	764	11.104	-13.926	-2.547	1.00	24.62	A
ATOM	1260	C	SER	A	764	12.274	-11.369	-1.687	1.00	21.35	A
ATOM	1261	O	SER	A	764	13.443	-11.319	-1.305	1.00	22.51	A
ATOM	1262	N	ASN	A	765	11.857	-10.746	-2.780	1.00	19.26	A
ATOM	1263	CA	ASN	A	765	12.790	-9.969	-3.571	1.00	19.42	A
ATOM	1264	CB	ASN	A	765	12.513	-10.164	-5.061	1.00	21.15	A
ATOM	1265	CG	ASN	A	765	12.836	-11.572	-5.524	1.00	24.10	A
ATOM	1266	OD1	ASN	A	765	13.910	-12.096	-5.210	1.00	27.80	A
ATOM	1267	ND2	ASN	A	765	11.917	-12.194	-6.271	1.00	26.16	A
ATOM	1268	C	ASN	A	765	12.738	-8.489	-3.198	1.00	19.25	A
ATOM	1269	O	ASN	A	765	13.266	-7.631	-3.915	1.00	19.32	A
ATOM	1270	N	LEU	A	766	12.125	-8.198	-2.053	1.00	15.23	A
ATOM	1271	CA	LEU	A	766	12.004	-6.830	-1.552	1.00	15.03	A
ATOM	1272	CB	LEU	A	766	13.386	-6.151	-1.451	1.00	14.51	A
ATOM	1273	CG	LEU	A	766	14.497	-6.907	-0.699	1.00	16.00	A
ATOM	1274	CD1	LEU	A	766	15.704	-5.956	-0.565	1.00	17.05	A
ATOM	1275	CD2	LEU	A	766	14.030	-7.346	0.691	1.00	17.26	A
ATOM	1276	C	LEU	A	766	11.054	-5.951	-2.376	1.00	13.94	A
ATOM	1277	O	LEU	A	766	11.021	-4.735	-2.196	1.00	13.56	A
ATOM	1278	N	VAL	A	767	10.289	-6.562	-3.279	1.00	12.87	A
ATOM	1279	CA	VAL	A	767	9.322	-5.808	-4.070	1.00	11.98	A
ATOM	1280	CB	VAL	A	767	8.714	-6.648	-5.202	1.00	9.61	A
ATOM	1281	CG1	VAL	A	767	7.574	-5.866	-5.857	1.00	9.58	A
ATOM	1282	CG2	VAL	A	767	9.783	-6.976	-6.240	1.00	9.18	A
ATOM	1283	C	VAL	A	767	8.190	-5.409	-3.130	1.00	13.34	A
ATOM	1284	O	VAL	A	767	7.635	-6.265	-2.436	1.00	12.17	A
ATOM	1285	N	CYS	A	768	7.860	-4.118	-3.099	1.00	12.87	A
ATOM	1286	CA	CYS	A	768	6.786	-3.594	-2.255	1.00	12.04	A
ATOM	1287	CB	CYS	A	768	7.213	-2.257	-1.649	1.00	12.99	A
ATOM	1288	SG	CYS	A	768	8.599	-2.417	-0.477	1.00	15.84	A
ATOM	1289	C	CYS	A	768	5.475	-3.421	-3.027	1.00	13.36	A
ATOM	1290	O	CYS	A	768	5.454	-2.834	-4.116	1.00	13.26	A
ATOM	1291	N	LYS	A	769	4.376	-3.894	-2.440	1.00	12.25	A
ATOM	1292	CA	LYS	A	769	3.073	-3.814	-3.101	1.00	12.28	A
ATOM	1293	CB	LYS	A	769	2.659	-5.209	-3.562	1.00	9.87	A
ATOM	1294	CG	LYS	A	769	3.672	-5.857	-4.462	1.00	13.00	A

ATOM	1295	CD	LYS	A	769	3.170	-7.163	-5.105	1.00	14.19	A
ATOM	1296	CE	LYS	A	769	4.242	-7.757	-6.022	1.00	16.77	A
ATOM	1297	NZ	LYS	A	769	3.710	-8.749	-6.980	1.00	16.50	A
ATOM	1298	C	LYS	A	769	1.978	-3.202	-2.245	1.00	13.01	A
ATOM	1299	O	LYS	A	769	1.844	-3.531	-1.063	1.00	14.29	A
ATOM	1300	N	VAL	A	770	1.184	-2.309	-2.835	1.00	12.10	A
ATOM	1301	CA	VAL	A	770	0.101	-1.677	-2.089	1.00	11.10	A
ATOM	1302	CB	VAL	A	770	-0.512	-0.499	-2.889	1.00	10.58	A
ATOM	1303	CG1	VAL	A	770	-1.644	0.112	-2.100	1.00	5.30	A
ATOM	1304	CG2	VAL	A	770	0.570	0.551	-3.186	1.00	6.99	A
ATOM	1305	C	VAL	A	770	-1.000	-2.696	-1.796	1.00	11.89	A
ATOM	1306	O	VAL	A	770	-1.353	-3.491	-2.662	1.00	12.00	A
ATOM	1307	N	SER	A	771	-1.527	-2.667	-0.576	1.00	11.80	A
ATOM	1308	CA	SER	A	771	-2.590	-3.578	-0.150	1.00	14.70	A
ATOM	1309	CB	SER	A	771	-2.002	-4.666	0.765	1.00	17.32	A
ATOM	1310	OG	SER	A	771	-2.990	-5.600	1.144	1.00	19.91	A
ATOM	1311	C	SER	A	771	-3.655	-2.795	0.630	1.00	14.68	A
ATOM	1312	O	SER	A	771	-3.709	-1.562	0.544	1.00	15.55	A
ATOM	1313	N	ASP	A	772	-4.508	-3.504	1.378	1.00	14.81	A
ATOM	1314	CA	ASP	A	772	-5.530	-2.865	2.212	1.00	16.39	A
ATOM	1315	CB	ASP	A	772	-4.852	-1.845	3.134	1.00	19.62	A
ATOM	1316	CG	ASP	A	772	-5.816	-1.172	4.110	1.00	22.71	A
ATOM	1317	OD1	ASP	A	772	-5.738	0.078	4.232	1.00	26.71	A
ATOM	1318	OD2	ASP	A	772	-6.622	-1.863	4.762	1.00	20.60	A
ATOM	1319	C	ASP	A	772	-6.633	-2.184	1.391	1.00	15.48	A
ATOM	1320	O	ASP	A	772	-6.867	-0.983	1.528	1.00	15.52	A
ATOM	1321	N	PHE	A	773	-7.302	-2.962	0.546	1.00	16.06	A
ATOM	1322	CA	PHE	A	773	-8.376	-2.449	-0.293	1.00	17.22	A
ATOM	1323	CB	PHE	A	773	-8.295	-3.087	-1.679	1.00	16.56	A
ATOM	1324	CG	PHE	A	773	-7.062	-2.696	-2.441	1.00	14.03	A
ATOM	1325	CD1	PHE	A	773	-6.005	-3.593	-2.611	1.00	12.33	A
ATOM	1326	CD2	PHE	A	773	-6.927	-1.396	-2.927	1.00	12.51	A
ATOM	1327	CE1	PHE	A	773	-4.824	-3.188	-3.251	1.00	14.35	A
ATOM	1328	CE2	PHE	A	773	-5.757	-0.989	-3.563	1.00	13.76	A
ATOM	1329	CZ	PHE	A	773	-4.706	-1.885	-3.723	1.00	11.63	A
ATOM	1330	C	PHE	A	773	-9.748	-2.693	0.325	1.00	21.10	A
ATOM	1331	O	PHE	A	773	-10.023	-3.784	0.824	1.00	25.25	A
ATOM	1332	N	PRO	A	797	-4.563	6.529	12.016	1.00	37.73	A
ATOM	1333	CD	PRO	A	797	-5.935	5.995	12.099	1.00	39.20	A
ATOM	1334	CA	PRO	A	797	-4.285	7.010	10.661	1.00	36.62	A
ATOM	1335	CB	PRO	A	797	-5.445	6.428	9.856	1.00	37.71	A
ATOM	1336	CG	PRO	A	797	-6.572	6.522	10.818	1.00	37.28	A
ATOM	1337	C	PRO	A	797	-4.206	8.537	10.558	1.00	34.49	A
ATOM	1338	O	PRO	A	797	-3.764	9.071	9.543	1.00	33.47	A
ATOM	1339	N	ILE	A	798	-4.629	9.236	11.609	1.00	32.85	A
ATOM	1340	CA	ILE	A	798	-4.588	10.695	11.606	1.00	29.61	A
ATOM	1341	CB	ILE	A	798	-4.905	11.269	12.997	1.00	30.95	A
ATOM	1342	CG2	ILE	A	798	-4.587	12.766	13.042	1.00	29.66	A
ATOM	1343	CG1	ILE	A	798	-6.373	11.020	13.327	1.00	29.77	A
ATOM	1344	CD1	ILE	A	798	-6.754	11.463	14.701	1.00	32.23	A
ATOM	1345	C	ILE	A	798	-3.241	11.252	11.157	1.00	28.44	A
ATOM	1346	O	ILE	A	798	-3.192	12.111	10.282	1.00	28.15	A
ATOM	1347	N	ARG	A	799	-2.154	10.768	11.752	1.00	26.63	A
ATOM	1348	CA	ARG	A	799	-0.818	11.247	11.403	1.00	26.62	A
ATOM	1349	CB	ARG	A	799	0.193	10.798	12.466	1.00	28.00	A
ATOM	1350	CG	ARG	A	799	0.416	9.294	12.553	1.00	28.23	A
ATOM	1351	CD	ARG	A	799	1.120	8.966	13.857	1.00	29.46	A
ATOM	1352	NE	ARG	A	799	0.298	9.380	14.993	1.00	30.72	A
ATOM	1353	CZ	ARG	A	799	0.771	9.878	16.129	1.00	30.22	A
ATOM	1354	NH1	ARG	A	799	2.074	10.036	16.303	1.00	28.37	A
ATOM	1355	NH2	ARG	A	799	-0.066	10.228	17.093	1.00	31.49	A
ATOM	1356	C	ARG	A	799	-0.350	10.789	10.018	1.00	24.48	A
ATOM	1357	O	ARG	A	799	0.781	11.053	9.622	1.00	24.93	A
ATOM	1358	N	TRP	A	800	-1.226	10.102	9.292	1.00	23.10	A

ATOM	1359	CA	TRP	A	800	-0.924	9.619	7.943	1.00	22.60	A
ATOM	1360	CB	TRP	A	800	-1.212	8.118	7.836	1.00	21.43	A
ATOM	1361	CG	TRP	A	800	-0.067	7.225	8.213	1.00	21.86	A
ATOM	1362	CD2	TRP	A	800	0.187	6.640	9.499	1.00	24.24	A
ATOM	1363	CE2	TRP	A	800	1.379	5.894	9.388	1.00	23.31	A
ATOM	1364	CE3	TRP	A	800	-0.477	6.673	10.734	1.00	24.72	A
ATOM	1365	CD1	TRP	A	800	0.953	6.822	7.404	1.00	20.84	A
ATOM	1366	NE1	TRP	A	800	1.824	6.023	8.099	1.00	21.54	A
ATOM	1367	CZ2	TRP	A	800	1.924	5.186	10.464	1.00	25.57	A
ATOM	1368	CZ3	TRP	A	800	0.067	5.966	11.807	1.00	26.76	A
ATOM	1369	CH2	TRP	A	800	1.255	5.234	11.662	1.00	25.91	A
ATOM	1370	C	TRP	A	800	-1.818	10.349	6.950	1.00	22.35	A
ATOM	1371	O	TRP	A	800	-1.623	10.276	5.741	1.00	22.75	A
ATOM	1372	N	THR	A	801	-2.805	11.054	7.480	1.00	22.40	A
ATOM	1373	CA	THR	A	801	-3.781	11.739	6.653	1.00	21.32	A
ATOM	1374	CB	THR	A	801	-5.177	11.517	7.242	1.00	20.93	A
ATOM	1375	OG1	THR	A	801	-5.356	10.114	7.520	1.00	19.55	A
ATOM	1376	CG2	THR	A	801	-6.253	11.971	6.264	1.00	19.42	A
ATOM	1377	C	THR	A	801	-3.521	13.224	6.483	1.00	22.83	A
ATOM	1378	O	THR	A	801	-3.073	13.901	7.405	1.00	24.26	A
ATOM	1379	N	ALA	A	802	-3.806	13.719	5.285	1.00	23.67	A
ATOM	1380	CA	ALA	A	802	-3.616	15.125	4.961	1.00	24.60	A
ATOM	1381	CB	ALA	A	802	-3.827	15.349	3.472	1.00	21.86	A
ATOM	1382	C	ALA	A	802	-4.567	16.006	5.755	1.00	25.32	A
ATOM	1383	O	ALA	A	802	-5.664	15.586	6.121	1.00	26.16	A
ATOM	1384	N	PRO	A	803	-4.155	17.250	6.032	1.00	26.55	A
ATOM	1385	CD	PRO	A	803	-2.823	17.825	5.768	1.00	25.55	A
ATOM	1386	CA	PRO	A	803	-4.991	18.183	6.791	1.00	27.54	A
ATOM	1387	CB	PRO	A	803	-4.158	19.462	6.789	1.00	29.43	A
ATOM	1388	CG	PRO	A	803	-2.743	18.934	6.788	1.00	29.14	A
ATOM	1389	C	PRO	A	803	-6.384	18.396	6.188	1.00	28.40	A
ATOM	1390	O	PRO	A	803	-7.387	18.318	6.897	1.00	28.43	A
ATOM	1391	N	GLU	A	804	-6.445	18.658	4.884	1.00	29.91	A
ATOM	1392	CA	GLU	A	804	-7.730	18.897	4.231	1.00	31.54	A
ATOM	1393	CB	GLU	A	804	-7.536	19.320	2.764	1.00	29.69	A
ATOM	1394	CG	GLU	A	804	-7.162	18.217	1.779	1.00	29.36	A
ATOM	1395	CD	GLU	A	804	-5.671	17.936	1.723	1.00	26.95	A
ATOM	1396	OE1	GLU	A	804	-4.921	18.476	2.563	1.00	26.91	A
ATOM	1397	OE2	GLU	A	804	-5.254	17.164	0.838	1.00	27.14	A
ATOM	1398	C	GLU	A	804	-8.634	17.671	4.318	1.00	32.75	A
ATOM	1399	O	GLU	A	804	-9.857	17.793	4.406	1.00	32.85	A
ATOM	1400	N	ALA	A	805	-8.022	16.492	4.314	1.00	34.37	A
ATOM	1401	CA	ALA	A	805	-8.768	15.244	4.397	1.00	36.04	A
ATOM	1402	CB	ALA	A	805	-7.859	14.069	4.054	1.00	36.25	A
ATOM	1403	C	ALA	A	805	-9.364	15.050	5.787	1.00	37.08	A
ATOM	1404	O	ALA	A	805	-10.422	14.444	5.942	1.00	37.44	A
ATOM	1405	N	ILE	A	806	-8.687	15.564	6.802	1.00	38.80	A
ATOM	1406	CA	ILE	A	806	-9.180	15.425	8.162	1.00	40.65	A
ATOM	1407	CB	ILE	A	806	-8.035	15.591	9.179	1.00	40.28	A
ATOM	1408	CG2	ILE	A	806	-8.582	15.572	10.601	1.00	39.56	A
ATOM	1409	CG1	ILE	A	806	-7.019	14.463	8.988	1.00	39.83	A
ATOM	1410	CD1	ILE	A	806	-5.798	14.585	9.870	1.00	41.52	A
ATOM	1411	C	ILE	A	806	-10.267	16.449	8.457	1.00	42.79	A
ATOM	1412	O	ILE	A	806	-11.265	16.137	9.108	1.00	42.39	A
ATOM	1413	N	GLN	A	807	-10.080	17.665	7.952	1.00	44.65	A
ATOM	1414	CA	GLN	A	807	-11.032	18.746	8.183	1.00	46.54	A
ATOM	1415	CB	GLN	A	807	-10.345	20.091	7.959	1.00	48.25	A
ATOM	1416	CG	GLN	A	807	-11.184	21.287	8.352	1.00	51.25	A
ATOM	1417	CD	GLN	A	807	-10.330	22.490	8.710	1.00	52.70	A
ATOM	1418	OE1	GLN	A	807	-9.503	22.940	7.914	1.00	52.66	A
ATOM	1419	NE2	GLN	A	807	-10.524	23.015	9.917	1.00	53.69	A
ATOM	1420	C	GLN	A	807	-12.306	18.679	7.348	1.00	47.43	A
ATOM	1421	O	GLN	A	807	-13.407	18.637	7.899	1.00	48.05	A
ATOM	1422	N	TYR	A	808	-12.161	18.673	6.025	1.00	48.14	A

ATOM	1423	CA	TYR	A	808	-13.319	18.630	5.134	1.00	47.86	A
ATOM	1424	CB	TYR	A	808	-13.151	19.628	3.981	1.00	49.76	A
ATOM	1425	CG	TYR	A	808	-12.690	21.004	4.407	1.00	51.92	A
ATOM	1426	CD1	TYR	A	808	-11.335	21.288	4.555	1.00	52.77	A
ATOM	1427	CE1	TYR	A	808	-10.905	22.540	4.976	1.00	54.43	A
ATOM	1428	CD2	TYR	A	808	-13.610	22.013	4.689	1.00	53.07	A
ATOM	1429	CE2	TYR	A	808	-13.191	23.271	5.113	1.00	54.30	A
ATOM	1430	CZ	TYR	A	808	-11.836	23.527	5.256	1.00	54.97	A
ATOM	1431	OH	TYR	A	808	-11.404	24.760	5.693	1.00	55.34	A
ATOM	1432	C	TYR	A	808	-13.556	17.244	4.547	1.00	46.87	A
ATOM	1433	O	TYR	A	808	-14.334	17.092	3.608	1.00	45.84	A
ATOM	1434	N	ARG	A	809	-12.884	16.240	5.103	1.00	45.55	A
ATOM	1435	CA	ARG	A	809	-13.004	14.863	4.632	1.00	44.26	A
ATOM	1436	CB	ARG	A	809	-14.346	14.259	5.060	1.00	45.12	A
ATOM	1437	CG	ARG	A	809	-14.499	14.086	6.563	0.00	45.61	A
ATOM	1438	CD	ARG	A	809	-15.764	13.313	6.903	0.00	46.19	A
ATOM	1439	NE	ARG	A	809	-15.851	13.007	8.328	0.00	46.63	A
ATOM	1440	CZ	ARG	A	809	-16.810	12.268	8.878	0.00	46.86	A
ATOM	1441	NH1	ARG	A	809	-17.771	11.756	8.122	0.00	47.00	A
ATOM	1442	NH2	ARG	A	809	-16.806	12.038	10.184	0.00	47.00	A
ATOM	1443	C	ARG	A	809	-12.849	14.761	3.115	1.00	42.45	A
ATOM	1444	O	ARG	A	809	-13.488	13.928	2.469	1.00	42.37	A
ATOM	1445	N	LYS	A	810	-11.992	15.610	2.557	1.00	40.09	A
ATOM	1446	CA	LYS	A	810	-11.737	15.617	1.120	1.00	38.13	A
ATOM	1447	CB	LYS	A	810	-11.373	17.030	0.649	1.00	39.28	A
ATOM	1448	CG	LYS	A	810	-12.443	18.075	0.917	1.00	41.84	A
ATOM	1449	CD	LYS	A	810	-12.071	19.415	0.293	1.00	43.21	A
ATOM	1450	CE	LYS	A	810	-13.210	20.414	0.425	1.00	43.84	A
ATOM	1451	NZ	LYS	A	810	-12.950	21.652	-0.356	1.00	44.49	A
ATOM	1452	C	LYS	A	810	-10.594	14.665	0.770	1.00	35.30	A
ATOM	1453	O	LYS	A	810	-9.429	15.050	0.826	1.00	34.59	A
ATOM	1454	N	PHE	A	811	-10.928	13.427	0.417	1.00	32.42	A
ATOM	1455	CA	PHE	A	811	-9.912	12.445	0.056	1.00	29.29	A
ATOM	1456	CB	PHE	A	811	-10.296	11.053	0.539	1.00	29.39	A
ATOM	1457	CG	PHE	A	811	-10.238	10.888	2.023	1.00	29.16	A
ATOM	1458	CD1	PHE	A	811	-11.317	11.258	2.822	1.00	30.55	A
ATOM	1459	CD2	PHE	A	811	-9.110	10.342	2.624	1.00	28.31	A
ATOM	1460	CE1	PHE	A	811	-11.273	11.078	4.202	1.00	31.51	A
ATOM	1461	CE2	PHE	A	811	-9.051	10.157	3.998	1.00	29.55	A
ATOM	1462	CZ	PHE	A	811	-10.135	10.526	4.792	1.00	31.35	A
ATOM	1463	C	PHE	A	811	-9.705	12.400	-1.444	1.00	27.52	A
ATOM	1464	O	PHE	A	811	-10.646	12.167	-2.198	1.00	26.39	A
ATOM	1465	N	THR	A	812	-8.462	12.617	-1.862	1.00	23.72	A
ATOM	1466	CA	THR	A	812	-8.089	12.617	-3.271	1.00	23.05	A
ATOM	1467	CB	THR	A	812	-7.970	14.054	-3.790	1.00	23.97	A
ATOM	1468	OG1	THR	A	812	-6.932	14.727	-3.067	1.00	23.73	A
ATOM	1469	CG2	THR	A	812	-9.283	14.818	-3.564	1.00	25.01	A
ATOM	1470	C	THR	A	812	-6.721	11.964	-3.424	1.00	21.01	A
ATOM	1471	O	THR	A	812	-6.102	11.577	-2.437	1.00	20.62	A
ATOM	1472	N	SER	A	813	-6.237	11.850	-4.655	1.00	20.38	A
ATOM	1473	CA	SER	A	813	-4.918	11.270	-4.859	1.00	20.11	A
ATOM	1474	CB	SER	A	813	-4.616	11.071	-6.350	1.00	18.76	A
ATOM	1475	OG	SER	A	813	-5.445	10.061	-6.898	1.00	18.07	A
ATOM	1476	C	SER	A	813	-3.872	12.185	-4.241	1.00	20.46	A
ATOM	1477	O	SER	A	813	-2.818	11.719	-3.809	1.00	19.84	A
ATOM	1478	N	ALA	A	814	-4.171	13.482	-4.178	1.00	19.76	A
ATOM	1479	CA	ALA	A	814	-3.239	14.450	-3.600	1.00	20.26	A
ATOM	1480	CB	ALA	A	814	-3.710	15.882	-3.875	1.00	19.22	A
ATOM	1481	C	ALA	A	814	-3.182	14.195	-2.110	1.00	19.65	A
ATOM	1482	O	ALA	A	814	-2.178	14.478	-1.446	1.00	18.61	A
ATOM	1483	N	SER	A	815	-4.289	13.691	-1.579	1.00	19.76	A
ATOM	1484	CA	SER	A	815	-4.355	13.364	-0.164	1.00	19.99	A
ATOM	1485	CB	SER	A	815	-5.803	13.086	0.244	1.00	19.81	A
ATOM	1486	OG	SER	A	815	-5.869	12.896	1.640	1.00	27.92	A

ATOM	1487	C	SER	A	815	-3.490	12.114	0.062	1.00 18.44	A
ATOM	1488	O	SER	A	815	-2.786	12.010	1.065	1.00 19.10	A
ATOM	1489	N	ASP	A	816	-3.544	11.169	-0.875	1.00 17.07	A
ATOM	1490	CA	ASP	A	816	-2.734	9.947	-0.774	1.00 15.75	A
ATOM	1491	CB	ASP	A	816	-3.041	8.953	-1.901	1.00 13.79	A
ATOM	1492	CG	ASP	A	816	-4.343	8.184	-1.691	1.00 12.11	A
ATOM	1493	OD1	ASP	A	816	-4.823	8.097	-0.543	1.00 14.33	A
ATOM	1494	OD2	ASP	A	816	-4.864	7.646	-2.685	1.00 13.38	A
ATOM	1495	C	ASP	A	816	-1.259	10.307	-0.887	1.00 16.60	A
ATOM	1496	O	ASP	A	816	-0.399	9.571	-0.392	1.00 14.48	A
ATOM	1497	N	VAL	A	817	-0.961	11.419	-1.557	1.00 13.18	A
ATOM	1498	CA	VAL	A	817	0.422	11.826	-1.721	1.00 13.34	A
ATOM	1499	CB	VAL	A	817	0.566	12.960	-2.788	1.00 11.51	A
ATOM	1500	CG1	VAL	A	817	1.944	13.589	-2.704	1.00 9.74	A
ATOM	1501	CG2	VAL	A	817	0.376	12.363	-4.179	1.00 11.50	A
ATOM	1502	C	VAL	A	817	1.005	12.286	-0.395	1.00 12.99	A
ATOM	1503	O	VAL	A	817	2.172	12.046	-0.108	1.00 13.15	A
ATOM	1504	N	TRP	A	818	0.189	12.938	0.421	1.00 14.23	A
ATOM	1505	CA	TRP	A	818	0.654	13.378	1.726	1.00 15.45	A
ATOM	1506	CB	TRP	A	818	-0.447	14.188	2.410	1.00 15.49	A
ATOM	1507	CG	TRP	A	818	-0.133	14.556	3.801	1.00 19.74	A
ATOM	1508	CD2	TRP	A	818	0.180	15.863	4.295	1.00 20.03	A
ATOM	1509	CE2	TRP	A	818	0.436	15.733	5.676	1.00 21.03	A
ATOM	1510	CE3	TRP	A	818	0.269	17.131	3.706	1.00 21.31	A
ATOM	1511	CD1	TRP	A	818	-0.060	13.715	4.869	1.00 19.62	A
ATOM	1512	NE1	TRP	A	818	0.283	14.410	5.998	1.00 21.47	A
ATOM	1513	CZ2	TRP	A	818	0.774	16.823	6.481	1.00 20.05	A
ATOM	1514	CZ3	TRP	A	818	0.606	18.217	4.506	1.00 19.00	A
ATOM	1515	CH2	TRP	A	818	0.854	18.055	5.878	1.00 20.15	A
ATOM	1516	C	TRP	A	818	0.996	12.121	2.531	1.00 15.99	A
ATOM	1517	O	TRP	A	818	2.033	12.048	3.210	1.00 15.51	A
ATOM	1518	N	SER	A	819	0.118	11.130	2.428	1.00 14.95	A
ATOM	1519	CA	SER	A	819	0.281	9.855	3.122	1.00 15.25	A
ATOM	1520	CB	SER	A	819	-0.929	8.950	2.852	1.00 14.79	A
ATOM	1521	OG	SER	A	819	-2.112	9.536	3.348	1.00 16.39	A
ATOM	1522	C	SER	A	819	1.550	9.181	2.629	1.00 14.02	A
ATOM	1523	O	SER	A	819	2.325	8.640	3.414	1.00 16.48	A
ATOM	1524	N	TYR	A	820	1.765	9.229	1.320	1.00 13.71	A
ATOM	1525	CA	TYR	A	820	2.956	8.636	0.726	1.00 14.58	A
ATOM	1526	CB	TYR	A	820	2.956	8.842	-0.799	1.00 13.45	A
ATOM	1527	CG	TYR	A	820	4.197	8.297	-1.453	1.00 12.89	A
ATOM	1528	CD1	TYR	A	820	4.336	6.931	-1.732	1.00 15.07	A
ATOM	1529	CE1	TYR	A	820	5.541	6.419	-2.219	1.00 12.78	A
ATOM	1530	CD2	TYR	A	820	5.285	9.128	-1.690	1.00 12.38	A
ATOM	1531	CE2	TYR	A	820	6.466	8.633	-2.166	1.00 11.32	A
ATOM	1532	CZ	TYR	A	820	6.600	7.288	-2.426	1.00 12.29	A
ATOM	1533	OH	TYR	A	820	7.814	6.840	-2.859	1.00 10.71	A
ATOM	1534	C	TYR	A	820	4.210	9.280	1.338	1.00 13.53	A
ATOM	1535	O	TYR	A	820	5.223	8.616	1.545	1.00 13.71	A
ATOM	1536	N	GLY	A	821	4.137	10.574	1.628	1.00 14.63	A
ATOM	1537	CA	GLY	A	821	5.275	11.245	2.218	1.00 13.52	A
ATOM	1538	C	GLY	A	821	5.563	10.662	3.585	1.00 14.77	A
ATOM	1539	O	GLY	A	821	6.719	10.454	3.959	1.00 13.85	A
ATOM	1540	N	ILE	A	822	4.509	10.408	4.347	1.00 15.25	A
ATOM	1541	CA	ILE	A	822	4.690	9.820	5.666	1.00 17.12	A
ATOM	1542	CB	ILE	A	822	3.344	9.674	6.420	1.00 17.21	A
ATOM	1543	CG2	ILE	A	822	3.569	9.002	7.768	1.00 17.52	A
ATOM	1544	CG1	ILE	A	822	2.689	11.050	6.577	1.00 17.04	A
ATOM	1545	CD1	ILE	A	822	3.528	12.069	7.309	1.00 15.74	A
ATOM	1546	C	ILE	A	822	5.326	8.443	5.495	1.00 15.76	A
ATOM	1547	O	ILE	A	822	6.174	8.059	6.293	1.00 17.81	A
ATOM	1548	N	VAL	A	823	4.920	7.710	4.457	1.00 13.84	A
ATOM	1549	CA	VAL	A	823	5.459	6.375	4.199	1.00 12.67	A
ATOM	1550	CB	VAL	A	823	4.738	5.711	2.989	1.00 12.77	A

ATOM	1551	CG1	VAL	A	823	5.403	4.386	2.633	1.00	10.23	A
ATOM	1552	CG2	VAL	A	823	3.271	5.494	3.328	1.00	13.23	A
ATOM	1553	C	VAL	A	823	6.961	6.454	3.918	1.00	14.16	A
ATOM	1554	O	VAL	A	823	7.745	5.594	4.339	1.00	12.18	A
ATOM	1555	N	MET	A	824	7.352	7.488	3.188	1.00	12.40	A
ATOM	1556	CA	MET	A	824	8.755	7.710	2.883	1.00	12.87	A
ATOM	1557	CB	MET	A	824	8.938	8.982	2.070	1.00	13.48	A
ATOM	1558	CG	MET	A	824	8.457	8.904	0.641	1.00	11.06	A
ATOM	1559	SD	MET	A	824	8.815	10.500	-0.170	1.00	15.45	A
ATOM	1560	CE	MET	A	824	10.625	10.460	-0.293	1.00	14.21	A
ATOM	1561	C	MET	A	824	9.506	7.876	4.181	1.00	11.22	A
ATOM	1562	O	MET	A	824	10.632	7.411	4.318	1.00	12.72	A
ATOM	1563	N	TRP	A	825	8.882	8.550	5.135	1.00	13.43	A
ATOM	1564	CA	TRP	A	825	9.532	8.760	6.416	1.00	16.39	A
ATOM	1565	CB	TRP	A	825	8.733	9.758	7.251	1.00	17.69	A
ATOM	1566	CG	TRP	A	825	9.485	10.300	8.429	1.00	21.01	A
ATOM	1567	CD2	TRP	A	825	9.404	9.836	9.783	1.00	22.74	A
ATOM	1568	CE2	TRP	A	825	10.267	10.646	10.556	1.00	24.73	A
ATOM	1569	CE3	TRP	A	825	8.686	8.816	10.417	1.00	24.55	A
ATOM	1570	CD1	TRP	A	825	10.372	11.338	8.433	1.00	22.10	A
ATOM	1571	NE1	TRP	A	825	10.842	11.554	9.708	1.00	23.09	A
ATOM	1572	CZ2	TRP	A	825	10.429	10.469	11.937	1.00	23.91	A
ATOM	1573	CZ3	TRP	A	825	8.848	8.641	11.791	1.00	24.02	A
ATOM	1574	CH2	TRP	A	825	9.713	9.464	12.532	1.00	24.58	A
ATOM	1575	C	TRP	A	825	9.651	7.415	7.143	1.00	16.44	A
ATOM	1576	O	TRP	A	825	10.718	7.074	7.648	1.00	15.71	A
ATOM	1577	N	GLU	A	826	8.564	6.645	7.185	1.00	15.79	A
ATOM	1578	CA	GLU	A	826	8.597	5.338	7.854	1.00	15.47	A
ATOM	1579	CB	GLU	A	826	7.266	4.609	7.685	1.00	15.67	A
ATOM	1580	CG	GLU	A	826	6.066	5.409	8.128	1.00	17.54	A
ATOM	1581	CD	GLU	A	826	4.797	4.603	8.027	1.00	17.43	A
ATOM	1582	OE1	GLU	A	826	4.561	3.760	8.918	1.00	17.18	A
ATOM	1583	OE2	GLU	A	826	4.047	4.793	7.054	1.00	19.83	A
ATOM	1584	C	GLU	A	826	9.698	4.459	7.297	1.00	15.72	A
ATOM	1585	O	GLU	A	826	10.430	3.809	8.043	1.00	14.73	A
ATOM	1586	N	VAL	A	827	9.807	4.448	5.973	1.00	14.75	A
ATOM	1587	CA	VAL	A	827	10.812	3.652	5.293	1.00	13.80	A
ATOM	1588	CB	VAL	A	827	10.605	3.688	3.776	1.00	13.84	A
ATOM	1589	CG1	VAL	A	827	11.864	3.166	3.064	1.00	15.75	A
ATOM	1590	CG2	VAL	A	827	9.395	2.845	3.404	1.00	12.52	A
ATOM	1591	C	VAL	A	827	12.241	4.107	5.598	1.00	15.22	A
ATOM	1592	O	VAL	A	827	13.114	3.282	5.855	1.00	15.68	A
ATOM	1593	N	MET	A	828	12.488	5.411	5.571	1.00	15.64	A
ATOM	1594	CA	MET	A	828	13.840	5.885	5.830	1.00	16.82	A
ATOM	1595	CB	MET	A	828	14.020	7.304	5.282	1.00	16.69	A
ATOM	1596	CG	MET	A	828	13.812	7.400	3.764	1.00	15.12	A
ATOM	1597	SD	MET	A	828	14.617	6.077	2.862	1.00	17.16	A
ATOM	1598	CE	MET	A	828	16.377	6.500	3.177	1.00	16.75	A
ATOM	1599	C	MET	A	828	14.182	5.815	7.319	1.00	17.74	A
ATOM	1600	O	MET	A	828	15.353	5.818	7.697	1.00	17.30	A
ATOM	1601	N	SER	A	829	13.146	5.731	8.146	1.00	16.25	A
ATOM	1602	CA	SER	A	829	13.287	5.639	9.602	1.00	19.49	A
ATOM	1603	CB	SER	A	829	12.129	6.360	10.296	1.00	19.11	A
ATOM	1604	OG	SER	A	829	12.153	7.747	10.028	1.00	26.80	A
ATOM	1605	C	SER	A	829	13.263	4.186	10.069	1.00	17.50	A
ATOM	1606	O	SER	A	829	13.340	3.921	11.264	1.00	19.93	A
ATOM	1607	N	TYR	A	830	13.157	3.265	9.118	1.00	15.75	A
ATOM	1608	CA	TYR	A	830	13.053	1.837	9.382	1.00	15.79	A
ATOM	1609	CB	TYR	A	830	14.364	1.250	9.930	1.00	15.94	A
ATOM	1610	CG	TYR	A	830	15.392	0.987	8.861	1.00	15.43	A
ATOM	1611	CD1	TYR	A	830	16.370	1.925	8.566	1.00	19.30	A
ATOM	1612	CE1	TYR	A	830	17.330	1.682	7.577	1.00	17.62	A
ATOM	1613	CD2	TYR	A	830	15.387	-0.202	8.141	1.00	15.96	A
ATOM	1614	CE2	TYR	A	830	16.332	-0.454	7.156	1.00	17.55	A

ATOM	1615	CZ	TYR	A	830	17.304	0.494	6.883	1.00	16.47	A
ATOM	1616	OH	TYR	A	830	18.260	0.225	5.930	1.00	15.91	A
ATOM	1617	C	TYR	A	830	11.889	1.459	10.298	1.00	16.77	A
ATOM	1618	O	TYR	A	830	12.051	0.715	11.273	1.00	14.45	A
ATOM	1619	N	GLY	A	831	10.707	1.979	9.979	1.00	14.09	A
ATOM	1620	CA	GLY	A	831	9.521	1.635	10.742	1.00	17.12	A
ATOM	1621	C	GLY	A	831	9.224	2.407	12.003	1.00	19.41	A
ATOM	1622	O	GLY	A	831	8.410	1.977	12.827	1.00	19.28	A
ATOM	1623	N	GLU	A	832	9.883	3.545	12.171	1.00	21.71	A
ATOM	1624	CA	GLU	A	832	9.633	4.365	13.340	1.00	23.50	A
ATOM	1625	CB	GLU	A	832	10.627	5.522	13.384	1.00	25.11	A
ATOM	1626	CG	GLU	A	832	10.396	6.521	14.496	1.00	26.95	A
ATOM	1627	CD	GLU	A	832	10.411	5.869	15.874	1.00	32.36	A
ATOM	1628	OE1	GLU	A	832	9.344	5.380	16.326	1.00	31.18	A
ATOM	1629	OE2	GLU	A	832	11.497	5.834	16.500	1.00	32.72	A
ATOM	1630	C	GLU	A	832	8.210	4.897	13.216	1.00	24.54	A
ATOM	1631	O	GLU	A	832	7.668	4.981	12.111	1.00	22.49	A
ATOM	1632	N	ARG	A	833	7.608	5.249	14.347	1.00	24.48	A
ATOM	1633	CA	ARG	A	833	6.252	5.780	14.351	1.00	26.11	A
ATOM	1634	CB	ARG	A	833	5.597	5.564	15.720	1.00	28.74	A
ATOM	1635	CG	ARG	A	833	4.146	6.014	15.794	1.00	31.71	A
ATOM	1636	CD	ARG	A	833	3.443	5.386	16.985	1.00	34.54	A
ATOM	1637	NE	ARG	A	833	2.023	5.716	17.036	1.00	36.70	A
ATOM	1638	CZ	ARG	A	833	1.538	6.853	17.521	1.00	38.93	A
ATOM	1639	NH1	ARG	A	833	2.360	7.776	17.998	1.00	40.22	A
ATOM	1640	NH2	ARG	A	833	0.230	7.063	17.538	1.00	39.85	A
ATOM	1641	C	ARG	A	833	6.280	7.266	14.019	1.00	26.85	A
ATOM	1642	O	ARG	A	833	7.007	8.038	14.641	1.00	28.24	A
ATOM	1643	N	PRO	A	834	5.495	7.683	13.018	1.00	25.28	A
ATOM	1644	CD	PRO	A	834	4.678	6.857	12.112	1.00	26.97	A
ATOM	1645	CA	PRO	A	834	5.450	9.090	12.624	1.00	24.70	A
ATOM	1646	CB	PRO	A	834	4.381	9.108	11.534	1.00	25.64	A
ATOM	1647	CG	PRO	A	834	4.533	7.759	10.896	1.00	24.55	A
ATOM	1648	C	PRO	A	834	5.086	9.984	13.802	1.00	25.05	A
ATOM	1649	O	PRO	A	834	4.091	9.742	14.487	1.00	23.06	A
ATOM	1650	N	TYR	A	835	5.902	11.013	14.023	1.00	26.38	A
ATOM	1651	CA	TYR	A	835	5.704	11.977	15.102	1.00	26.19	A
ATOM	1652	CB	TYR	A	835	4.303	12.584	15.002	1.00	26.82	A
ATOM	1653	CG	TYR	A	835	4.015	13.202	13.648	1.00	27.32	A
ATOM	1654	CD1	TYR	A	835	4.405	14.511	13.358	1.00	26.52	A
ATOM	1655	CE1	TYR	A	835	4.175	15.069	12.101	1.00	26.25	A
ATOM	1656	CD2	TYR	A	835	3.387	12.464	12.647	1.00	25.35	A
ATOM	1657	CE2	TYR	A	835	3.153	13.008	11.386	1.00	25.46	A
ATOM	1658	CZ	TYR	A	835	3.550	14.314	11.116	1.00	26.18	A
ATOM	1659	OH	TYR	A	835	3.325	14.859	9.867	1.00	25.65	A
ATOM	1660	C	TYR	A	835	5.933	11.349	16.477	1.00	27.36	A
ATOM	1661	O	TYR	A	835	5.554	11.912	17.505	1.00	28.19	A
ATOM	1662	N	TRP	A	836	6.554	10.174	16.475	1.00	26.91	A
ATOM	1663	CA	TRP	A	836	6.885	9.454	17.699	1.00	28.58	A
ATOM	1664	CB	TRP	A	836	8.097	10.114	18.356	1.00	27.99	A
ATOM	1665	CG	TRP	A	836	9.233	10.282	17.406	1.00	29.96	A
ATOM	1666	CD2	TRP	A	836	9.533	11.449	16.631	1.00	29.72	A
ATOM	1667	CE2	TRP	A	836	10.666	11.149	15.847	1.00	30.62	A
ATOM	1668	CE3	TRP	A	836	8.953	12.722	16.525	1.00	31.28	A
ATOM	1669	CD1	TRP	A	836	10.169	9.346	17.069	1.00	29.72	A
ATOM	1670	NE1	TRP	A	836	11.034	9.859	16.133	1.00	29.17	A
ATOM	1671	CZ2	TRP	A	836	11.235	12.076	14.965	1.00	30.51	A
ATOM	1672	CZ3	TRP	A	836	9.520	13.646	15.648	1.00	30.96	A
ATOM	1673	CH2	TRP	A	836	10.649	13.315	14.882	1.00	31.70	A
ATOM	1674	C	TRP	A	836	5.727	9.370	18.688	1.00	29.62	A
ATOM	1675	O	TRP	A	836	4.627	8.945	18.328	1.00	29.84	A
ATOM	1676	N	ASP	A	837	5.977	9.789	19.927	1.00	31.12	A
ATOM	1677	CA	ASP	A	837	4.972	9.743	20.992	1.00	34.13	A
ATOM	1678	CB	ASP	A	837	5.659	9.720	22.365	1.00	34.74	A

ATOM	1679	CG	ASP	A	837	6.593	8.536	22.533	0.00	35.23	A
ATOM	1680	OD1	ASP	A	837	6.132	7.384	22.389	0.00	35.57	A
ATOM	1681	OD2	ASP	A	837	7.790	8.758	22.811	0.00	35.57	A
ATOM	1682	C	ASP	A	837	3.954	10.879	20.969	1.00	35.08	A
ATOM	1683	O	ASP	A	837	3.129	10.998	21.875	1.00	35.37	A
ATOM	1684	N	MET	A	838	4.009	11.722	19.946	1.00	36.64	A
ATOM	1685	CA	MET	A	838	3.056	12.821	19.845	1.00	37.58	A
ATOM	1686	CB	MET	A	838	3.315	13.648	18.594	1.00	37.74	A
ATOM	1687	CG	MET	A	838	4.207	14.831	18.800	1.00	37.49	A
ATOM	1688	SD	MET	A	838	4.120	15.864	17.349	1.00	40.87	A
ATOM	1689	CE	MET	A	838	5.651	15.422	16.541	1.00	37.80	A
ATOM	1690	C	MET	A	838	1.638	12.295	19.771	1.00	38.85	A
ATOM	1691	O	MET	A	838	1.392	11.235	19.196	1.00	38.49	A
ATOM	1692	N	THR	A	839	0.708	13.052	20.345	1.00	40.77	A
ATOM	1693	CA	THR	A	839	-0.707	12.691	20.332	1.00	42.26	A
ATOM	1694	CB	THR	A	839	-1.470	13.372	21.493	1.00	42.77	A
ATOM	1695	OG1	THR	A	839	-1.599	14.773	21.224	0.00	42.95	A
ATOM	1696	CG2	THR	A	839	-0.719	13.188	22.806	0.00	42.95	A
ATOM	1697	C	THR	A	839	-1.289	13.184	19.007	1.00	42.46	A
ATOM	1698	O	THR	A	839	-0.688	14.030	18.348	1.00	42.49	A
ATOM	1699	N	ASN	A	840	-2.450	12.660	18.616	1.00	43.26	A
ATOM	1700	CA	ASN	A	840	-3.078	13.075	17.363	1.00	44.27	A
ATOM	1701	CB	ASN	A	840	-4.419	12.360	17.154	1.00	43.58	A
ATOM	1702	CG	ASN	A	840	-4.256	10.885	16.855	1.00	43.42	A
ATOM	1703	OD1	ASN	A	840	-3.230	10.460	16.328	1.00	42.91	A
ATOM	1704	ND2	ASN	A	840	-5.278	10.097	17.172	1.00	44.00	A
ATOM	1705	C	ASN	A	840	-3.299	14.585	17.327	1.00	44.84	A
ATOM	1706	O	ASN	A	840	-3.017	15.236	16.321	1.00	45.54	A
ATOM	1707	N	GLN	A	841	-3.798	15.141	18.427	1.00	45.95	A
ATOM	1708	CA	GLN	A	841	-4.046	16.573	18.497	1.00	46.24	A
ATOM	1709	CB	GLN	A	841	-4.718	16.947	19.818	1.00	47.54	A
ATOM	1710	CG	GLN	A	841	-5.283	18.356	19.818	1.00	48.27	A
ATOM	1711	CD	GLN	A	841	-6.207	18.594	18.638	1.00	49.43	A
ATOM	1712	OE1	GLN	A	841	-7.199	17.884	18.460	1.00	49.85	A
ATOM	1713	NE2	GLN	A	841	-5.882	19.591	17.820	1.00	49.98	A
ATOM	1714	C	GLN	A	841	-2.744	17.347	18.350	1.00	46.35	A
ATOM	1715	O	GLN	A	841	-2.702	18.373	17.673	1.00	46.78	A
ATOM	1716	N	ASP	A	842	-1.682	16.861	18.984	1.00	45.35	A
ATOM	1717	CA	ASP	A	842	-0.396	17.531	18.878	1.00	45.11	A
ATOM	1718	CB	ASP	A	842	0.651	16.836	19.745	1.00	47.46	A
ATOM	1719	CG	ASP	A	842	0.324	16.913	21.224	1.00	49.71	A
ATOM	1720	OD1	ASP	A	842	-0.182	17.971	21.667	1.00	50.47	A
ATOM	1721	OD2	ASP	A	842	0.583	15.923	21.942	1.00	50.96	A
ATOM	1722	C	ASP	A	842	0.059	17.535	17.424	1.00	43.89	A
ATOM	1723	O	ASP	A	842	0.540	18.549	16.923	1.00	43.19	A
ATOM	1724	N	VAL	A	843	-0.099	16.397	16.752	1.00	42.58	A
ATOM	1725	CA	VAL	A	843	0.285	16.281	15.351	1.00	41.17	A
ATOM	1726	CB	VAL	A	843	-0.012	14.869	14.795	1.00	41.26	A
ATOM	1727	CG1	VAL	A	843	0.278	14.828	13.308	1.00	39.84	A
ATOM	1728	CG2	VAL	A	843	0.831	13.829	15.530	1.00	41.01	A
ATOM	1729	C	VAL	A	843	-0.481	17.301	14.518	1.00	40.78	A
ATOM	1730	O	VAL	A	843	0.103	18.029	13.714	1.00	38.98	A
ATOM	1731	N	ILE	A	844	-1.795	17.340	14.717	1.00	40.52	A
ATOM	1732	CA	ILE	A	844	-2.657	18.269	14.003	1.00	41.21	A
ATOM	1733	CB	ILE	A	844	-4.123	18.129	14.470	1.00	40.73	A
ATOM	1734	CG2	ILE	A	844	-4.995	19.190	13.800	1.00	40.70	A
ATOM	1735	CG1	ILE	A	844	-4.625	16.716	14.160	1.00	40.24	A
ATOM	1736	CD1	ILE	A	844	-6.004	16.413	14.694	1.00	39.42	A
ATOM	1737	C	ILE	A	844	-2.196	19.706	14.237	1.00	42.20	A
ATOM	1738	O	ILE	A	844	-2.035	20.478	13.289	1.00	42.32	A
ATOM	1739	N	ASN	A	845	-1.988	20.059	15.502	1.00	42.47	A
ATOM	1740	CA	ASN	A	845	-1.550	21.405	15.845	1.00	43.99	A
ATOM	1741	CB	ASN	A	845	-1.525	21.606	17.361	1.00	45.43	A
ATOM	1742	CG	ASN	A	845	-2.885	21.417	17.998	1.00	46.85	A

ATOM	1743	OD1	ASN	A	845	-3.903	21.851	17.458	1.00	47.77	A
ATOM	1744	ND2	ASN	A	845	-2.908	20.779	19.163	1.00	48.25	A
ATOM	1745	C	ASN	A	845	-0.162	21.664	15.286	1.00	43.59	A
ATOM	1746	O	ASN	A	845	0.123	22.750	14.784	1.00	43.60	A
ATOM	1747	N	ALA	A	846	0.702	20.660	15.376	1.00	42.78	A
ATOM	1748	CA	ALA	A	846	2.057	20.793	14.870	1.00	42.00	A
ATOM	1749	CB	ALA	A	846	2.829	19.497	15.092	1.00	41.98	A
ATOM	1750	C	ALA	A	846	2.021	21.142	13.386	1.00	41.78	A
ATOM	1751	O	ALA	A	846	2.662	22.100	12.954	1.00	41.69	A
ATOM	1752	N	ILE	A	847	1.269	20.364	12.609	1.00	41.74	A
ATOM	1753	CA	ILE	A	847	1.155	20.600	11.173	1.00	41.99	A
ATOM	1754	CB	ILE	A	847	0.250	19.540	10.492	1.00	41.47	A
ATOM	1755	CG2	ILE	A	847	0.083	19.863	9.013	1.00	41.65	A
ATOM	1756	CG1	ILE	A	847	0.869	18.148	10.641	1.00	41.58	A
ATOM	1757	CD1	ILE	A	847	2.243	18.014	10.006	1.00	41.53	A
ATOM	1758	C	ILE	A	847	0.584	21.990	10.906	1.00	42.01	A
ATOM	1759	O	ILE	A	847	1.032	22.685	9.996	1.00	41.61	A
ATOM	1760	N	GLU	A	848	-0.402	22.388	11.704	1.00	42.81	A
ATOM	1761	CA	GLU	A	848	-1.022	23.700	11.563	1.00	43.79	A
ATOM	1762	CB	GLU	A	848	-2.158	23.866	12.576	1.00	43.97	A
ATOM	1763	CG	GLU	A	848	-3.380	23.013	12.281	0.00	44.75	A
ATOM	1764	CD	GLU	A	848	-4.518	23.276	13.247	0.00	45.09	A
ATOM	1765	OE1	GLU	A	848	-4.985	24.432	13.317	0.00	45.34	A
ATOM	1766	OE2	GLU	A	848	-4.947	22.326	13.935	0.00	45.34	A
ATOM	1767	C	GLU	A	848	0.011	24.806	11.760	1.00	44.25	A
ATOM	1768	O	GLU	A	848	-0.033	25.830	11.082	1.00	44.97	A
ATOM	1769	N	GLN	A	849	0.939	24.588	12.689	1.00	43.53	A
ATOM	1770	CA	GLN	A	849	1.997	25.552	12.974	1.00	43.30	A
ATOM	1771	CB	GLN	A	849	2.554	25.328	14.380	1.00	43.26	A
ATOM	1772	CG	GLN	A	849	1.549	25.528	15.492	0.00	44.28	A
ATOM	1773	CD	GLN	A	849	1.042	26.951	15.557	0.00	44.64	A
ATOM	1774	OE1	GLN	A	849	1.816	27.889	15.745	0.00	44.94	A
ATOM	1775	NE2	GLN	A	849	-0.264	27.121	15.399	0.00	44.94	A
ATOM	1776	C	GLN	A	849	3.126	25.402	11.959	1.00	43.40	A
ATOM	1777	O	GLN	A	849	4.252	25.842	12.199	1.00	43.15	A
ATOM	1778	N	ASP	A	850	2.814	24.770	10.830	1.00	43.13	A
ATOM	1779	CA	ASP	A	850	3.780	24.545	9.760	1.00	42.79	A
ATOM	1780	CB	ASP	A	850	4.287	25.888	9.222	1.00	43.87	A
ATOM	1781	CG	ASP	A	850	3.260	26.586	8.350	1.00	45.00	A
ATOM	1782	OD1	ASP	A	850	2.980	26.080	7.245	1.00	47.53	A
ATOM	1783	OD2	ASP	A	850	2.724	27.634	8.767	1.00	45.98	A
ATOM	1784	C	ASP	A	850	4.957	23.652	10.162	1.00	41.93	A
ATOM	1785	O	ASP	A	850	6.064	23.796	9.651	1.00	42.38	A
ATOM	1786	N	TYR	A	851	4.709	22.718	11.073	1.00	40.80	A
ATOM	1787	CA	TYR	A	851	5.752	21.795	11.512	1.00	39.73	A
ATOM	1788	CB	TYR	A	851	5.481	21.311	12.930	1.00	39.91	A
ATOM	1789	CG	TYR	A	851	6.348	20.139	13.323	1.00	39.84	A
ATOM	1790	CD1	TYR	A	851	7.674	20.327	13.710	1.00	40.12	A
ATOM	1791	CE1	TYR	A	851	8.478	19.249	14.062	1.00	39.79	A
ATOM	1792	CD2	TYR	A	851	5.847	18.837	13.294	1.00	40.19	A
ATOM	1793	CE2	TYR	A	851	6.643	17.751	13.642	1.00	39.38	A
ATOM	1794	CZ	TYR	A	851	7.955	17.964	14.027	1.00	39.62	A
ATOM	1795	OH	TYR	A	851	8.742	16.899	14.388	1.00	36.75	A
ATOM	1796	C	TYR	A	851	5.811	20.577	10.592	1.00	37.96	A
ATOM	1797	O	TYR	A	851	4.778	20.053	10.185	1.00	39.15	A
ATOM	1798	N	ARG	A	852	7.018	20.127	10.273	1.00	35.12	A
ATOM	1799	CA	ARG	A	852	7.185	18.961	9.419	1.00	33.58	A
ATOM	1800	CB	ARG	A	852	7.568	19.394	8.003	1.00	32.00	A
ATOM	1801	CG	ARG	A	852	6.478	20.173	7.287	1.00	31.55	A
ATOM	1802	CD	ARG	A	852	5.271	19.293	7.006	1.00	29.23	A
ATOM	1803	NE	ARG	A	852	4.254	19.976	6.206	1.00	30.58	A
ATOM	1804	CZ	ARG	A	852	3.358	20.835	6.688	1.00	28.76	A
ATOM	1805	NH1	ARG	A	852	3.336	21.132	7.980	1.00	27.10	A
ATOM	1806	NH2	ARG	A	852	2.476	21.393	5.876	1.00	28.74	A

ATOM	1807	C	ARG	A	852	8.253	18.033	9.992	1.00	32.81	A
ATOM	1808	O	ARG	A	852	9.260	18.490	10.524	1.00	33.32	A
ATOM	1809	N	LEU	A	853	8.025	16.729	9.881	1.00	31.16	A
ATOM	1810	CA	LEU	A	853	8.963	15.741	10.392	1.00	29.31	A
ATOM	1811	CB	LEU	A	853	8.493	14.330	10.040	1.00	28.71	A
ATOM	1812	CG	LEU	A	853	7.220	13.837	10.730	1.00	31.23	A
ATOM	1813	CD1	LEU	A	853	6.775	12.514	10.090	1.00	29.70	A
ATOM	1814	CD2	LEU	A	853	7.472	13.662	12.227	1.00	31.09	A
ATOM	1815	C	LEU	A	853	10.360	15.959	9.832	1.00	29.46	A
ATOM	1816	O	LEU	A	853	10.534	16.191	8.633	1.00	27.80	A
ATOM	1817	N	PRO	A	854	11.379	15.878	10.700	1.00	29.14	A
ATOM	1818	CD	PRO	A	854	11.277	15.586	12.144	1.00	29.31	A
ATOM	1819	CA	PRO	A	854	12.775	16.063	10.302	1.00	29.67	A
ATOM	1820	CB	PRO	A	854	13.487	16.207	11.641	1.00	29.68	A
ATOM	1821	CG	PRO	A	854	12.715	15.259	12.514	1.00	29.75	A
ATOM	1822	C	PRO	A	854	13.278	14.861	9.511	1.00	29.68	A
ATOM	1823	O	PRO	A	854	12.659	13.803	9.520	1.00	29.00	A
ATOM	1824	N	PRO	A	855	14.415	15.008	8.820	1.00	30.63	A
ATOM	1825	CD	PRO	A	855	15.242	16.220	8.668	1.00	30.11	A
ATOM	1826	CA	PRO	A	855	14.965	13.897	8.040	1.00	30.85	A
ATOM	1827	CB	PRO	A	855	16.089	14.561	7.246	1.00	31.70	A
ATOM	1828	CG	PRO	A	855	16.548	15.653	8.163	1.00	29.94	A
ATOM	1829	C	PRO	A	855	15.479	12.757	8.919	1.00	32.90	A
ATOM	1830	O	PRO	A	855	16.201	12.990	9.886	1.00	33.00	A
ATOM	1831	N	PRO	A	856	15.092	11.508	8.602	1.00	33.31	A
ATOM	1832	CD	PRO	A	856	14.065	11.113	7.620	1.00	32.70	A
ATOM	1833	CA	PRO	A	856	15.542	10.348	9.380	1.00	34.07	A
ATOM	1834	CB	PRO	A	856	14.894	9.172	8.649	1.00	33.02	A
ATOM	1835	CG	PRO	A	856	13.617	9.767	8.158	1.00	33.24	A
ATOM	1836	C	PRO	A	856	17.073	10.258	9.374	1.00	34.59	A
ATOM	1837	O	PRO	A	856	17.732	10.793	8.484	1.00	34.67	A
ATOM	1838	N	MET	A	857	17.633	9.571	10.363	1.00	35.13	A
ATOM	1839	CA	MET	A	857	19.081	9.429	10.467	1.00	34.34	A
ATOM	1840	CB	MET	A	857	19.432	8.523	11.650	1.00	34.60	A
ATOM	1841	CG	MET	A	857	20.891	8.620	12.117	1.00	36.07	A
ATOM	1842	SD	MET	A	857	21.222	7.511	13.500	0.00	36.17	A
ATOM	1843	CE	MET	A	857	20.786	8.554	14.888	0.00	36.58	A
ATOM	1844	C	MET	A	857	19.673	8.865	9.178	1.00	33.94	A
ATOM	1845	O	MET	A	857	19.195	7.858	8.643	1.00	32.79	A
ATOM	1846	N	ASP	A	858	20.713	9.533	8.685	1.00	32.95	A
ATOM	1847	CA	ASP	A	858	21.398	9.120	7.463	1.00	32.12	A
ATOM	1848	CB	ASP	A	858	21.957	7.697	7.631	1.00	33.12	A
ATOM	1849	CG	ASP	A	858	22.948	7.591	8.778	0.00	33.41	A
ATOM	1850	OD1	ASP	A	858	23.981	8.292	8.740	0.00	33.74	A
ATOM	1851	OD2	ASP	A	858	22.694	6.809	9.719	0.00	33.74	A
ATOM	1852	C	ASP	A	858	20.500	9.181	6.227	1.00	30.87	A
ATOM	1853	O	ASP	A	858	20.787	8.546	5.212	1.00	31.21	A
ATOM	1854	N	CYS	A	859	19.420	9.951	6.299	1.00	29.14	A
ATOM	1855	CA	CYS	A	859	18.514	10.056	5.158	1.00	28.23	A
ATOM	1856	CB	CYS	A	859	17.091	10.370	5.620	1.00	27.03	A
ATOM	1857	SG	CYS	A	859	15.950	10.675	4.219	1.00	25.20	A
ATOM	1858	C	CYS	A	859	18.951	11.128	4.172	1.00	26.49	A
ATOM	1859	O	CYS	A	859	19.063	12.297	4.535	1.00	27.20	A
ATOM	1860	N	PRO	A	860	19.187	10.747	2.905	1.00	25.74	A
ATOM	1861	CD	PRO	A	860	19.019	9.402	2.329	1.00	25.44	A
ATOM	1862	CA	PRO	A	860	19.610	11.703	1.877	1.00	25.49	A
ATOM	1863	CB	PRO	A	860	19.450	10.911	0.584	1.00	26.82	A
ATOM	1864	CG	PRO	A	860	19.754	9.518	1.013	1.00	25.74	A
ATOM	1865	C	PRO	A	860	18.750	12.965	1.875	1.00	25.80	A
ATOM	1866	O	PRO	A	860	17.528	12.887	2.037	1.00	23.12	A
ATOM	1867	N	SER	A	861	19.383	14.123	1.685	1.00	24.04	A
ATOM	1868	CA	SER	A	861	18.651	15.390	1.661	1.00	24.93	A
ATOM	1869	CB	SER	A	861	19.597	16.579	1.437	1.00	24.17	A
ATOM	1870	OG	SER	A	861	20.464	16.754	2.533	1.00	28.72	A

ATOM	1871	C	SER	A	861	17.596	15.405	0.558	1.00	22.46	A
ATOM	1872	O	SER	A	861	16.491	15.887	0.765	1.00	23.97	A
ATOM	1873	N	ALA	A	862	17.937	14.886	-0.612	1.00	22.99	A
ATOM	1874	CA	ALA	A	862	16.990	14.879	-1.715	1.00	23.51	A
ATOM	1875	CB	ALA	A	862	17.626	14.254	-2.962	1.00	25.30	A
ATOM	1876	C	ALA	A	862	15.720	14.121	-1.327	1.00	23.45	A
ATOM	1877	O	ALA	A	862	14.619	14.549	-1.667	1.00	22.65	A
ATOM	1878	N	LEU	A	863	15.870	13.004	-0.615	1.00	21.36	A
ATOM	1879	CA	LEU	A	863	14.703	12.232	-0.186	1.00	20.64	A
ATOM	1880	CB	LEU	A	863	15.110	10.907	0.470	1.00	17.21	A
ATOM	1881	CG	LEU	A	863	15.473	9.807	-0.522	1.00	17.62	A
ATOM	1882	CD1	LEU	A	863	15.995	8.573	0.220	1.00	19.11	A
ATOM	1883	CD2	LEU	A	863	14.236	9.465	-1.353	1.00	18.32	A
ATOM	1884	C	LEU	A	863	13.821	13.010	0.774	1.00	19.07	A
ATOM	1885	O	LEU	A	863	12.595	13.005	0.641	1.00	20.62	A
ATOM	1886	N	HIS	A	864	14.434	13.683	1.741	1.00	19.85	A
ATOM	1887	CA	HIS	A	864	13.643	14.448	2.686	1.00	18.66	A
ATOM	1888	CB	HIS	A	864	14.496	14.954	3.847	1.00	19.81	A
ATOM	1889	CG	HIS	A	864	13.700	15.626	4.922	1.00	19.98	A
ATOM	1890	CD2	HIS	A	864	12.826	15.127	5.828	1.00	20.76	A
ATOM	1891	ND1	HIS	A	864	13.735	16.988	5.133	1.00	21.33	A
ATOM	1892	CE1	HIS	A	864	12.919	17.299	6.125	1.00	22.47	A
ATOM	1893	NE2	HIS	A	864	12.355	16.187	6.564	1.00	22.76	A
ATOM	1894	C	HIS	A	864	12.988	15.619	1.983	1.00	19.62	A
ATOM	1895	O	HIS	A	864	11.897	16.052	2.366	1.00	19.61	A
ATOM	1896	N	GLN	A	865	13.641	16.143	0.952	1.00	19.53	A
ATOM	1897	CA	GLN	A	865	13.039	17.259	0.238	1.00	19.79	A
ATOM	1898	CB	GLN	A	865	13.977	17.808	-0.837	1.00	19.80	A
ATOM	1899	CG	GLN	A	865	13.379	18.989	-1.567	1.00	21.23	A
ATOM	1900	CD	GLN	A	865	13.013	20.114	-0.618	1.00	22.98	A
ATOM	1901	OE1	GLN	A	865	13.868	20.627	0.105	1.00	26.38	A
ATOM	1902	NE2	GLN	A	865	11.739	20.504	-0.613	1.00	21.44	A
ATOM	1903	C	GLN	A	865	11.766	16.750	-0.416	1.00	19.00	A
ATOM	1904	O	GLN	A	865	10.735	17.419	-0.396	1.00	19.67	A
ATOM	1905	N	LEU	A	866	11.841	15.559	-0.997	1.00	19.26	A
ATOM	1906	CA	LEU	A	866	10.663	14.988	-1.632	1.00	18.45	A
ATOM	1907	CB	LEU	A	866	11.014	13.649	-2.283	1.00	18.07	A
ATOM	1908	CG	LEU	A	866	9.887	12.930	-3.021	1.00	19.78	A
ATOM	1909	CD1	LEU	A	866	9.168	13.903	-3.967	1.00	18.91	A
ATOM	1910	CD2	LEU	A	866	10.467	11.754	-3.775	1.00	20.97	A
ATOM	1911	C	LEU	A	866	9.546	14.824	-0.589	1.00	18.47	A
ATOM	1912	O	LEU	A	866	8.367	15.026	-0.890	1.00	17.51	A
ATOM	1913	N	MET	A	867	9.921	14.476	0.641	1.00	18.09	A
ATOM	1914	CA	MET	A	867	8.946	14.318	1.711	1.00	18.01	A
ATOM	1915	CB	MET	A	867	9.632	13.865	3.005	1.00	19.66	A
ATOM	1916	CG	MET	A	867	10.077	12.419	2.991	1.00	20.12	A
ATOM	1917	SD	MET	A	867	10.968	11.976	4.495	1.00	22.40	A
ATOM	1918	CE	MET	A	867	12.235	10.954	3.814	1.00	22.54	A
ATOM	1919	C	MET	A	867	8.228	15.640	1.965	1.00	18.98	A
ATOM	1920	O	MET	A	867	6.996	15.686	2.058	1.00	17.83	A
ATOM	1921	N	LEU	A	868	9.007	16.712	2.089	1.00	18.92	A
ATOM	1922	CA	LEU	A	868	8.447	18.042	2.326	1.00	20.03	A
ATOM	1923	CB	LEU	A	868	9.566	19.083	2.455	1.00	21.62	A
ATOM	1924	CG	LEU	A	868	10.538	18.913	3.628	1.00	22.08	A
ATOM	1925	CD1	LEU	A	868	11.607	20.012	3.578	1.00	21.68	A
ATOM	1926	CD2	LEU	A	868	9.772	18.989	4.942	1.00	18.97	A
ATOM	1927	C	LEU	A	868	7.506	18.444	1.191	1.00	19.33	A
ATOM	1928	O	LEU	A	868	6.501	19.111	1.420	1.00	20.63	A
ATOM	1929	N	ASP	A	869	7.836	18.037	-0.031	1.00	17.79	A
ATOM	1930	CA	ASP	A	869	7.001	18.360	-1.183	1.00	18.56	A
ATOM	1931	CB	ASP	A	869	7.707	17.971	-2.484	1.00	17.65	A
ATOM	1932	CG	ASP	A	869	8.988	18.762	-2.703	1.00	18.80	A
ATOM	1933	OD1	ASP	A	869	9.175	19.790	-2.021	1.00	16.81	A
ATOM	1934	OD2	ASP	A	869	9.799	18.364	-3.557	1.00	18.79	A

ATOM	1935	C	ASP	A	869	5.664	17.651	-1.072	1.00	20.40	A
ATOM	1936	O	ASP	A	869	4.631	18.197	-1.460	1.00	21.71	A
ATOM	1937	N	CYS	A	870	5.682	16.439	-0.524	1.00	18.78	A
ATOM	1938	CA	CYS	A	870	4.456	15.670	-0.354	1.00	19.36	A
ATOM	1939	CB	CYS	A	870	4.769	14.201	-0.039	1.00	15.21	A
ATOM	1940	SG	CYS	A	870	5.477	13.278	-1.422	1.00	17.93	A
ATOM	1941	C	CYS	A	870	3.616	16.256	0.769	1.00	18.15	A
ATOM	1942	O	CYS	A	870	2.390	16.090	0.785	1.00	20.18	A
ATOM	1943	N	TRP	A	871	4.259	16.956	1.702	1.00	19.04	A
ATOM	1944	CA	TRP	A	871	3.529	17.534	2.833	1.00	20.40	A
ATOM	1945	CB	TRP	A	871	4.306	17.335	4.151	1.00	20.01	A
ATOM	1946	CG	TRP	A	871	4.663	15.890	4.480	1.00	21.12	A
ATOM	1947	CD2	TRP	A	871	5.874	15.424	5.095	1.00	19.64	A
ATOM	1948	CE2	TRP	A	871	5.778	14.014	5.204	1.00	18.64	A
ATOM	1949	CE3	TRP	A	871	7.029	16.060	5.563	1.00	18.54	A
ATOM	1950	CD1	TRP	A	871	3.897	14.770	4.254	1.00	21.26	A
ATOM	1951	NE1	TRP	A	871	4.567	13.642	4.685	1.00	19.40	A
ATOM	1952	CZ2	TRP	A	871	6.797	13.232	5.762	1.00	18.78	A
ATOM	1953	CZ3	TRP	A	871	8.045	15.282	6.120	1.00	19.69	A
ATOM	1954	CH2	TRP	A	871	7.920	13.878	6.214	1.00	19.97	A
ATOM	1955	C	TRP	A	871	3.168	19.012	2.669	1.00	20.88	A
ATOM	1956	O	TRP	A	871	2.999	19.736	3.654	1.00	21.06	A
ATOM	1957	N	GLN	A	872	3.055	19.459	1.424	1.00	22.74	A
ATOM	1958	CA	GLN	A	872	2.680	20.846	1.157	1.00	25.25	A
ATOM	1959	CB	GLN	A	872	2.768	21.158	-0.337	1.00	23.93	A
ATOM	1960	CG	GLN	A	872	4.174	21.383	-0.816	1.00	29.27	A
ATOM	1961	CD	GLN	A	872	4.857	22.495	-0.047	1.00	32.45	A
ATOM	1962	OE1	GLN	A	872	4.377	23.628	-0.015	1.00	34.77	A
ATOM	1963	NE2	GLN	A	872	5.979	22.178	0.579	1.00	35.29	A
ATOM	1964	C	GLN	A	872	1.260	21.073	1.639	1.00	25.69	A
ATOM	1965	O	GLN	A	872	0.351	20.310	1.301	1.00	26.55	A
ATOM	1966	N	LYS	A	873	1.081	22.112	2.445	1.00	26.47	A
ATOM	1967	CA	LYS	A	873	-0.224	22.463	2.990	1.00	27.95	A
ATOM	1968	CB	LYS	A	873	-0.139	23.849	3.639	1.00	28.61	A
ATOM	1969	CG	LYS	A	873	-1.390	24.304	4.360	1.00	29.84	A
ATOM	1970	CD	LYS	A	873	-1.188	25.685	4.968	0.00	30.40	A
ATOM	1971	CE	LYS	A	873	-2.412	26.130	5.752	0.00	30.90	A
ATOM	1972	NZ	LYS	A	873	-2.223	27.477	6.360	0.00	31.23	A
ATOM	1973	C	LYS	A	873	-1.281	22.446	1.886	1.00	29.41	A
ATOM	1974	O	LYS	A	873	-2.320	21.800	2.022	1.00	28.03	A
ATOM	1975	N	ASP	A	874	-1.008	23.156	0.793	1.00	30.47	A
ATOM	1976	CA	ASP	A	874	-1.930	23.211	-0.340	1.00	32.13	A
ATOM	1977	CB	ASP	A	874	-1.585	24.399	-1.247	1.00	34.07	A
ATOM	1978	CG	ASP	A	874	-2.640	24.656	-2.304	1.00	36.22	A
ATOM	1979	OD1	ASP	A	874	-3.160	23.678	-2.887	1.00	36.33	A
ATOM	1980	OD2	ASP	A	874	-2.944	25.844	-2.560	1.00	38.96	A
ATOM	1981	C	ASP	A	874	-1.806	21.919	-1.146	1.00	30.91	A
ATOM	1982	O	ASP	A	874	-0.758	21.653	-1.727	1.00	30.73	A
ATOM	1983	N	ARG	A	875	-2.876	21.134	-1.207	1.00	30.76	A
ATOM	1984	CA	ARG	A	875	-2.837	19.870	-1.939	1.00	30.91	A
ATOM	1985	CB	ARG	A	875	-4.177	19.138	-1.832	1.00	32.82	A
ATOM	1986	CG	ARG	A	875	-5.316	19.755	-2.635	1.00	35.08	A
ATOM	1987	CD	ARG	A	875	-6.413	18.722	-2.844	1.00	40.15	A
ATOM	1988	NE	ARG	A	875	-7.555	19.234	-3.603	1.00	43.73	A
ATOM	1989	CZ	ARG	A	875	-8.448	20.094	-3.125	1.00	45.20	A
ATOM	1990	NH1	ARG	A	875	-8.334	20.544	-1.883	1.00	45.87	A
ATOM	1991	NH2	ARG	A	875	-9.457	20.502	-3.885	1.00	47.30	A
ATOM	1992	C	ARG	A	875	-2.477	20.028	-3.412	1.00	28.33	A
ATOM	1993	O	ARG	A	875	-1.965	19.100	-4.033	1.00	26.80	A
ATOM	1994	N	ASN	A	876	-2.756	21.199	-3.972	1.00	27.63	A
ATOM	1995	CA	ASN	A	876	-2.463	21.457	-5.375	1.00	27.11	A
ATOM	1996	CB	ASN	A	876	-3.223	22.703	-5.845	1.00	29.67	A
ATOM	1997	CG	ASN	A	876	-4.663	22.396	-6.237	1.00	32.23	A
ATOM	1998	OD1	ASN	A	876	-5.558	23.221	-6.060	1.00	36.30	A

ATOM	1999	ND2	ASN	A	876	-4.887	21.212	-6.786	1.00	33.53	A
ATOM	2000	C	ASN	A	876	-0.972	21.621	-5.632	1.00	25.93	A
ATOM	2001	O	ASN	A	876	-0.500	21.396	-6.746	1.00	26.98	A
ATOM	2002	N	HIS	A	877	-0.235	21.996	-4.592	1.00	24.62	A
ATOM	2003	CA	HIS	A	877	1.206	22.203	-4.690	1.00	23.95	A
ATOM	2004	CB	HIS	A	877	1.666	23.185	-3.605	1.00	25.91	A
ATOM	2005	CG	HIS	A	877	1.103	24.566	-3.758	1.00	28.62	A
ATOM	2006	CD2	HIS	A	877	0.390	25.134	-4.760	1.00	29.02	A
ATOM	2007	ND1	HIS	A	877	1.268	25.548	-2.803	1.00	30.92	A
ATOM	2008	CE1	HIS	A	877	0.682	26.659	-3.212	1.00	32.07	A
ATOM	2009	NE2	HIS	A	877	0.142	26.434	-4.396	1.00	30.42	A
ATOM	2010	C	HIS	A	877	1.987	20.893	-4.555	1.00	24.02	A
ATOM	2011	O	HIS	A	877	3.169	20.821	-4.919	1.00	21.47	A
ATOM	2012	N	ARG	A	878	1.342	19.860	-4.017	1.00	22.45	A
ATOM	2013	CA	ARG	A	878	2.022	18.574	-3.858	1.00	20.77	A
ATOM	2014	CB	ARG	A	878	1.196	17.618	-2.995	1.00	18.58	A
ATOM	2015	CG	ARG	A	878	0.878	18.140	-1.609	1.00	17.53	A
ATOM	2016	CD	ARG	A	878	-0.163	17.267	-0.922	1.00	17.61	A
ATOM	2017	NE	ARG	A	878	-0.678	17.923	0.273	1.00	15.99	A
ATOM	2018	CZ	ARG	A	878	-1.898	17.746	0.763	1.00	17.79	A
ATOM	2019	NH1	ARG	A	878	-2.743	16.913	0.165	1.00	18.10	A
ATOM	2020	NH2	ARG	A	878	-2.282	18.440	1.830	1.00	20.88	A
ATOM	2021	C	ARG	A	878	2.264	17.922	-5.208	1.00	20.33	A
ATOM	2022	O	ARG	A	878	1.473	18.058	-6.137	1.00	21.44	A
ATOM	2023	N	PRO	A	879	3.377	17.200	-5.334	1.00	19.46	A
ATOM	2024	CD	PRO	A	879	4.395	16.893	-4.307	1.00	20.47	A
ATOM	2025	CA	PRO	A	879	3.687	16.530	-6.592	1.00	18.32	A
ATOM	2026	CB	PRO	A	879	5.116	16.050	-6.374	1.00	19.77	A
ATOM	2027	CG	PRO	A	879	5.106	15.696	-4.907	1.00	18.07	A
ATOM	2028	C	PRO	A	879	2.727	15.362	-6.801	1.00	18.71	A
ATOM	2029	O	PRO	A	879	2.135	14.846	-5.849	1.00	17.95	A
ATOM	2030	N	LYS	A	880	2.569	14.957	-8.051	1.00	18.17	A
ATOM	2031	CA	LYS	A	880	1.705	13.835	-8.373	1.00	19.50	A
ATOM	2032	CB	LYS	A	880	1.118	14.000	-9.775	1.00	20.53	A
ATOM	2033	CG	LYS	A	880	0.082	15.125	-9.888	1.00	23.92	A
ATOM	2034	CD	LYS	A	880	-0.316	15.362	-11.334	1.00	26.32	A
ATOM	2035	CE	LYS	A	880	-1.444	16.384	-11.434	1.00	29.77	A
ATOM	2036	NZ	LYS	A	880	-1.732	16.761	-12.845	1.00	33.61	A
ATOM	2037	C	LYS	A	880	2.545	12.572	-8.315	1.00	18.71	A
ATOM	2038	O	LYS	A	880	3.775	12.637	-8.369	1.00	15.94	A
ATOM	2039	N	PHE	A	881	1.887	11.421	-8.207	1.00	19.36	A
ATOM	2040	CA	PHE	A	881	2.625	10.174	-8.148	1.00	18.63	A
ATOM	2041	CB	PHE	A	881	1.679	8.980	-7.961	1.00	18.14	A
ATOM	2042	CG	PHE	A	881	1.154	8.856	-6.561	1.00	15.85	A
ATOM	2043	CD1	PHE	A	881	-0.182	9.091	-6.281	1.00	15.19	A
ATOM	2044	CD2	PHE	A	881	2.017	8.573	-5.503	1.00	14.91	A
ATOM	2045	CE1	PHE	A	881	-0.661	9.055	-4.974	1.00	14.06	A
ATOM	2046	CE2	PHE	A	881	1.545	8.536	-4.186	1.00	14.78	A
ATOM	2047	CZ	PHE	A	881	0.201	8.780	-3.923	1.00	16.56	A
ATOM	2048	C	PHE	A	881	3.500	9.975	-9.365	1.00	18.17	A
ATOM	2049	O	PHE	A	881	4.570	9.381	-9.266	1.00	17.98	A
ATOM	2050	N	GLY	A	882	3.065	10.476	-10.517	1.00	17.95	A
ATOM	2051	CA	GLY	A	882	3.879	10.329	-11.710	1.00	17.50	A
ATOM	2052	C	GLY	A	882	5.173	11.112	-11.559	1.00	17.01	A
ATOM	2053	O	GLY	A	882	6.256	10.660	-11.953	1.00	15.84	A
ATOM	2054	N	GLN	A	883	5.066	12.295	-10.974	1.00	16.68	A
ATOM	2055	CA	GLN	A	883	6.240	13.129	-10.776	1.00	18.91	A
ATOM	2056	CB	GLN	A	883	5.813	14.551	-10.391	1.00	19.76	A
ATOM	2057	CG	GLN	A	883	4.850	15.188	-11.387	1.00	25.47	A
ATOM	2058	CD	GLN	A	883	4.415	16.571	-10.949	1.00	26.44	A
ATOM	2059	OE1	GLN	A	883	3.799	16.739	-9.896	1.00	24.34	A
ATOM	2060	NE2	GLN	A	883	4.748	17.577	-11.756	1.00	28.51	A
ATOM	2061	C	GLN	A	883	7.116	12.519	-9.677	1.00	17.08	A
ATOM	2062	O	GLN	A	883	8.336	12.625	-9.719	1.00	16.89	A

ATOM	2063	N	ILE	A	884	6.484	11.872	-8.700	1.00	16.63	A
ATOM	2064	CA	ILE	A	884	7.221	11.240	-7.612	1.00	15.31	A
ATOM	2065	CB	ILE	A	884	6.267	10.698	-6.516	1.00	16.28	A
ATOM	2066	CG2	ILE	A	884	7.001	9.708	-5.594	1.00	15.49	A
ATOM	2067	CG1	ILE	A	884	5.700	11.869	-5.714	1.00	15.76	A
ATOM	2068	CD1	ILE	A	884	4.588	11.471	-4.743	1.00	19.15	A
ATOM	2069	C	ILE	A	884	8.058	10.102	-8.166	1.00	14.47	A
ATOM	2070	O	ILE	A	884	9.229	9.988	-7.839	1.00	14.80	A
ATOM	2071	N	VAL	A	885	7.466	9.275	-9.024	1.00	13.59	A
ATOM	2072	CA	VAL	A	885	8.223	8.177	-9.601	1.00	16.17	A
ATOM	2073	CB	VAL	A	885	7.352	7.284	-10.502	1.00	16.96	A
ATOM	2074	CG1	VAL	A	885	8.216	6.248	-11.178	1.00	15.86	A
ATOM	2075	CG2	VAL	A	885	6.252	6.588	-9.676	1.00	16.66	A
ATOM	2076	C	VAL	A	885	9.414	8.683	-10.416	1.00	19.15	A
ATOM	2077	O	VAL	A	885	10.479	8.062	-10.417	1.00	16.03	A
ATOM	2078	N	ASN	A	886	9.241	9.808	-11.110	1.00	19.66	A
ATOM	2079	CA	ASN	A	886	10.320	10.343	-11.936	1.00	21.37	A
ATOM	2080	CB	ASN	A	886	9.819	11.509	-12.793	1.00	23.10	A
ATOM	2081	CG	ASN	A	886	8.698	11.102	-13.734	1.00	26.10	A
ATOM	2082	OD1	ASN	A	886	8.773	10.056	-14.398	1.00	26.24	A
ATOM	2083	ND2	ASN	A	886	7.654	11.926	-13.804	1.00	27.46	A
ATOM	2084	C	ASN	A	886	11.500	10.807	-11.097	1.00	20.89	A
ATOM	2085	O	ASN	A	886	12.655	10.562	-11.446	1.00	21.26	A
ATOM	2086	N	THR	A	887	11.189	11.479	-9.995	1.00	19.17	A
ATOM	2087	CA	THR	A	887	12.180	11.991	-9.069	1.00	20.28	A
ATOM	2088	CB	THR	A	887	11.500	12.789	-7.939	1.00	22.23	A
ATOM	2089	OG1	THR	A	887	10.751	13.872	-8.504	1.00	24.34	A
ATOM	2090	CG2	THR	A	887	12.525	13.327	-6.968	1.00	22.10	A
ATOM	2091	C	THR	A	887	12.961	10.838	-8.450	1.00	20.51	A
ATOM	2092	O	THR	A	887	14.182	10.906	-8.339	1.00	20.72	A
ATOM	2093	N	LEU	A	888	12.259	9.778	-8.055	1.00	17.54	A
ATOM	2094	CA	LEU	A	888	12.926	8.619	-7.458	1.00	16.74	A
ATOM	2095	CB	LEU	A	888	11.906	7.629	-6.882	1.00	13.99	A
ATOM	2096	CG	LEU	A	888	11.102	8.102	-5.660	1.00	16.09	A
ATOM	2097	CD1	LEU	A	888	9.998	7.118	-5.344	1.00	12.23	A
ATOM	2098	CD2	LEU	A	888	12.037	8.236	-4.444	1.00	15.84	A
ATOM	2099	C	LEU	A	888	13.791	7.939	-8.507	1.00	17.83	A
ATOM	2100	O	LEU	A	888	14.914	7.509	-8.215	1.00	16.99	A
ATOM	2101	N	ASP	A	889	13.278	7.846	-9.731	1.00	18.45	A
ATOM	2102	CA	ASP	A	889	14.047	7.231	-10.809	1.00	19.88	A
ATOM	2103	CB	ASP	A	889	13.216	7.089	-12.092	1.00	20.92	A
ATOM	2104	CG	ASP	A	889	12.212	5.954	-12.031	1.00	24.40	A
ATOM	2105	OD1	ASP	A	889	12.496	4.901	-11.417	1.00	23.95	A
ATOM	2106	OD2	ASP	A	889	11.127	6.106	-12.620	1.00	26.43	A
ATOM	2107	C	ASP	A	889	15.303	8.053	-11.128	1.00	20.04	A
ATOM	2108	O	ASP	A	889	16.341	7.491	-11.459	1.00	20.12	A
ATOM	2109	N	LYS	A	890	15.221	9.377	-11.035	1.00	20.98	A
ATOM	2110	CA	LYS	A	890	16.398	10.193	-11.320	1.00	24.03	A
ATOM	2111	CB	LYS	A	890	16.042	11.679	-11.353	1.00	23.49	A
ATOM	2112	CG	LYS	A	890	15.102	12.062	-12.480	0.00	24.55	A
ATOM	2113	CD	LYS	A	890	14.792	13.544	-12.453	0.00	25.01	A
ATOM	2114	CE	LYS	A	890	13.901	13.935	-13.615	0.00	25.39	A
ATOM	2115	NZ	LYS	A	890	13.587	15.388	-13.598	0.00	25.67	A
ATOM	2116	C	LYS	A	890	17.455	9.935	-10.255	1.00	23.54	A
ATOM	2117	O	LYS	A	890	18.644	9.911	-10.555	1.00	23.88	A
ATOM	2118	N	MET	A	891	17.014	9.744	-9.012	1.00	23.82	A
ATOM	2119	CA	MET	A	891	17.939	9.457	-7.913	1.00	22.98	A
ATOM	2120	CB	MET	A	891	17.192	9.425	-6.573	1.00	22.51	A
ATOM	2121	CG	MET	A	891	16.487	10.746	-6.206	1.00	19.86	A
ATOM	2122	SD	MET	A	891	15.428	10.557	-4.742	1.00	22.11	A
ATOM	2123	CE	MET	A	891	15.002	12.246	-4.390	1.00	18.78	A
ATOM	2124	C	MET	A	891	18.639	8.120	-8.163	1.00	23.81	A
ATOM	2125	O	MET	A	891	19.853	8.009	-7.996	1.00	23.38	A
ATOM	2126	N	ILE	A	892	17.874	7.113	-8.581	1.00	22.60	A

ATOM	2127	CA	ILE	A	892	18.451	5.806	-8.853	1.00	23.72	A
ATOM	2128	CB	ILE	A	892	17.362	4.765	-9.203	1.00	22.69	A
ATOM	2129	CG2	ILE	A	892	18.001	3.453	-9.665	1.00	21.79	A
ATOM	2130	CG1	ILE	A	892	16.501	4.487	-7.969	1.00	21.70	A
ATOM	2131	CD1	ILE	A	892	15.347	3.569	-8.236	1.00	21.58	A
ATOM	2132	C	ILE	A	892	19.454	5.892	-10.004	1.00	25.56	A
ATOM	2133	O	ILE	A	892	20.508	5.264	-9.964	1.00	24.56	A
ATOM	2134	N	ARG	A	893	19.126	6.672	-11.029	1.00	27.68	A
ATOM	2135	CA	ARG	A	893	20.006	6.826	-12.183	1.00	28.93	A
ATOM	2136	CB	ARG	A	893	19.246	7.486	-13.338	1.00	29.77	A
ATOM	2137	CG	ARG	A	893	18.033	6.702	-13.801	0.00	30.52	A
ATOM	2138	CD	ARG	A	893	17.167	7.518	-14.745	0.00	31.20	A
ATOM	2139	NE	ARG	A	893	16.022	6.747	-15.220	0.00	31.76	A
ATOM	2140	CZ	ARG	A	893	15.065	7.231	-16.006	0.00	32.04	A
ATOM	2141	NH1	ARG	A	893	15.109	8.492	-16.413	0.00	32.22	A
ATOM	2142	NH2	ARG	A	893	14.065	6.449	-16.388	0.00	32.22	A
ATOM	2143	C	ARG	A	893	21.237	7.659	-11.828	1.00	28.29	A
ATOM	2144	O	ARG	A	893	22.304	7.472	-12.410	1.00	30.73	A
ATOM	2145	N	ASN	A	894	21.090	8.574	-10.873	1.00	27.77	A
ATOM	2146	CA	ASN	A	894	22.206	9.421	-10.454	1.00	28.66	A
ATOM	2147	CB	ASN	A	894	21.928	10.883	-10.791	1.00	32.18	A
ATOM	2148	CG	ASN	A	894	21.446	11.064	-12.204	1.00	35.93	A
ATOM	2149	OD1	ASN	A	894	20.309	10.708	-12.536	1.00	38.24	A
ATOM	2150	ND2	ASN	A	894	22.305	11.613	-13.056	1.00	37.07	A
ATOM	2151	C	ASN	A	894	22.444	9.295	-8.960	1.00	27.18	A
ATOM	2152	O	ASN	A	894	22.256	10.257	-8.205	1.00	24.38	A
ATOM	2153	N	PRO	A	895	22.878	8.102	-8.517	1.00	27.24	A
ATOM	2154	CD	PRO	A	895	23.287	6.996	-9.402	1.00	27.14	A
ATOM	2155	CA	PRO	A	895	23.162	7.774	-7.116	1.00	27.82	A
ATOM	2156	CB	PRO	A	895	23.990	6.496	-7.222	1.00	27.28	A
ATOM	2157	CG	PRO	A	895	23.441	5.847	-8.435	1.00	29.74	A
ATOM	2158	C	PRO	A	895	23.888	8.859	-6.324	1.00	27.80	A
ATOM	2159	O	PRO	A	895	23.705	8.974	-5.112	1.00	26.04	A
ATOM	2160	N	ASN	A	896	24.718	9.655	-6.988	1.00	29.72	A
ATOM	2161	CA	ASN	A	896	25.426	10.694	-6.257	1.00	31.84	A
ATOM	2162	CB	ASN	A	896	26.449	11.392	-7.152	1.00	35.12	A
ATOM	2163	CG	ASN	A	896	27.619	10.495	-7.491	1.00	37.45	A
ATOM	2164	OD1	ASN	A	896	28.189	9.842	-6.610	1.00	37.32	A
ATOM	2165	ND2	ASN	A	896	27.988	10.455	-8.769	1.00	38.75	A
ATOM	2166	C	ASN	A	896	24.471	11.715	-5.652	1.00	31.58	A
ATOM	2167	O	ASN	A	896	24.789	12.337	-4.642	1.00	32.05	A
ATOM	2168	N	SER	A	897	23.295	11.876	-6.250	1.00	31.96	A
ATOM	2169	CA	SER	A	897	22.322	12.828	-5.724	1.00	31.92	A
ATOM	2170	CB	SER	A	897	21.100	12.903	-6.639	1.00	32.67	A
ATOM	2171	OG	SER	A	897	20.427	11.657	-6.699	1.00	32.92	A
ATOM	2172	C	SER	A	897	21.872	12.442	-4.320	1.00	32.25	A
ATOM	2173	O	SER	A	897	21.288	13.253	-3.601	1.00	32.16	A
ATOM	2174	N	LEU	A	898	22.150	11.200	-3.939	1.00	32.39	A
ATOM	2175	CA	LEU	A	898	21.767	10.684	-2.629	1.00	33.14	A
ATOM	2176	CB	LEU	A	898	21.338	9.223	-2.755	1.00	31.76	A
ATOM	2177	CG	LEU	A	898	20.167	8.938	-3.702	1.00	30.43	A
ATOM	2178	CD1	LEU	A	898	20.050	7.442	-3.949	1.00	28.81	A
ATOM	2179	CD2	LEU	A	898	18.886	9.489	-3.101	1.00	29.32	A
ATOM	2180	C	LEU	A	898	22.915	10.791	-1.633	1.00	35.96	A
ATOM	2181	O	LEU	A	898	22.780	10.410	-0.466	1.00	35.50	A
ATOM	2182	N	LYS	A	899	24.049	11.304	-2.100	1.00	37.16	A
ATOM	2183	CA	LYS	A	899	25.218	11.453	-1.245	1.00	39.32	A
ATOM	2184	CB	LYS	A	899	26.458	11.783	-2.083	1.00	39.91	A
ATOM	2185	CG	LYS	A	899	26.875	10.675	-3.035	1.00	40.95	A
ATOM	2186	CD	LYS	A	899	27.176	9.392	-2.279	1.00	42.25	A
ATOM	2187	CE	LYS	A	899	27.521	8.254	-3.230	1.00	43.26	A
ATOM	2188	NZ	LYS	A	899	27.655	6.962	-2.498	1.00	43.52	A
ATOM	2189	C	LYS	A	899	24.996	12.540	-0.204	1.00	39.53	A
ATOM	2190	O	LYS	A	899	25.502	12.451	0.913	1.00	39.99	A

ATOM	2191	N	ALA	A	900	24.238	13.566	-0.574	1.00	40.31	A
ATOM	2192	CA	ALA	A	900	23.952	14.672	0.332	1.00	41.45	A
ATOM	2193	CB	ALA	A	900	23.297	15.816	-0.436	1.00	42.71	A
ATOM	2194	C	ALA	A	900	23.047	14.225	1.477	1.00	42.06	A
ATOM	2195	O	ALA	A	900	23.462	14.222	2.638	1.00	43.54	A
ATOM	2196	O	HOH	A	1	14.457	-2.301	-3.629	1.00	11.91	A
ATOM	2197	O	HOH	A	2	-4.397	11.098	3.237	1.00	16.01	A
ATOM	2198	O	HOH	A	3	-4.918	7.667	-5.486	1.00	16.02	A
ATOM	2199	O	HOH	A	4	-18.623	-6.192	-4.002	1.00	15.98	A
ATOM	2200	O	HOH	A	5	-1.021	11.333	-8.745	1.00	17.20	A
ATOM	2201	O	HOH	A	6	2.429	1.976	9.154	1.00	11.10	A
ATOM	2202	O	HOH	A	7	9.183	-2.818	-7.644	1.00	12.10	A
ATOM	2203	O	HOH	A	8	-2.277	-6.184	-9.377	1.00	16.99	A
ATOM	2204	O	HOH	A	9	-3.892	7.522	2.129	1.00	11.77	A
ATOM	2205	O	HOH	A	10	-24.765	-1.312	-3.431	1.00	11.31	A
ATOM	2206	O	HOH	A	11	-18.960	-7.652	-1.790	1.00	14.87	A
ATOM	2207	O	HOH	A	12	1.251	-7.943	-7.973	1.00	15.91	A
ATOM	2208	O	HOH	A	13	-5.135	9.220	4.569	1.00	25.85	A
ATOM	2209	O	HOH	A	14	0.868	13.830	8.869	1.00	19.70	A
ATOM	2210	O	HOH	A	15	-4.469	-6.600	-8.030	1.00	17.02	A
ATOM	2211	O	HOH	A	16	-23.949	2.424	-2.051	1.00	16.20	A
ATOM	2212	O	HOH	A	17	16.570	-0.194	-6.147	1.00	20.96	A
ATOM	2213	O	HOH	A	18	0.212	10.493	-11.249	1.00	32.03	A
ATOM	2214	O	HOH	A	19	18.352	-5.806	-3.576	1.00	21.26	A
ATOM	2215	O	HOH	A	20	-1.189	18.011	-6.297	1.00	21.54	A
ATOM	2216	O	HOH	A	21	-2.174	-6.079	3.946	1.00	21.58	A
ATOM	2217	O	HOH	A	22	2.660	2.991	-12.285	1.00	10.78	A
ATOM	2218	O	HOH	A	23	6.194	0.599	12.618	1.00	26.49	A
ATOM	2219	O	HOH	A	24	6.270	2.873	10.787	1.00	20.59	A
ATOM	2220	O	HOH	A	25	-30.350	-2.848	-5.086	1.00	21.38	A
ATOM	2221	O	HOH	A	26	-5.973	10.069	1.056	1.00	21.49	A
ATOM	2222	O	HOH	A	27	7.351	-13.578	-1.294	1.00	24.35	A
ATOM	2223	O	HOH	A	28	-16.655	-18.205	6.142	1.00	32.77	A
ATOM	2224	O	HOH	A	29	-23.065	-6.820	10.522	1.00	24.13	A
ATOM	2225	O	HOH	A	30	14.170	15.934	-4.146	1.00	22.96	A
ATOM	2226	O	HOH	A	31	-5.570	-1.784	-15.428	1.00	26.29	A
ATOM	2227	O	HOH	A	32	-12.382	-1.657	-13.385	1.00	22.13	A
ATOM	2228	O	HOH	A	33	11.773	-2.825	-3.978	1.00	17.40	A
ATOM	2229	O	HOH	A	34	24.033	2.469	1.013	1.00	28.57	A
ATOM	2230	O	HOH	A	35	5.376	16.007	8.519	1.00	24.65	A
ATOM	2231	O	HOH	A	36	-9.608	-13.304	-9.571	1.00	27.67	A
ATOM	2232	O	HOH	A	37	-5.225	-8.904	-9.144	1.00	18.25	A
ATOM	2233	O	HOH	A	38	11.257	-0.407	-7.511	1.00	29.30	A
ATOM	2234	O	HOH	A	39	0.499	-15.307	-6.874	1.00	26.00	A
ATOM	2235	O	HOH	A	40	-11.598	-8.243	3.065	1.00	18.53	A
ATOM	2236	O	HOH	A	41	2.939	23.776	3.343	1.00	30.46	A
ATOM	2237	O	HOH	A	42	-10.147	-9.966	7.681	1.00	26.73	A
ATOM	2238	O	HOH	A	43	9.258	-2.252	-4.749	1.00	18.60	A
ATOM	2239	O	HOH	A	44	-7.990	1.495	0.072	1.00	32.79	A
ATOM	2240	O	HOH	A	45	-21.791	-2.653	3.395	1.00	30.17	A
ATOM	2241	O	HOH	A	46	-12.258	8.515	-1.865	1.00	32.59	A
ATOM	2242	O	HOH	A	47	17.934	-29.751	44.878	1.00	37.91	A
ATOM	2243	O	HOH	A	48	-5.849	14.783	-6.753	1.00	25.08	A
ATOM	2244	O	HOH	A	49	-0.415	-15.909	-10.041	1.00	30.96	A
ATOM	2245	O	HOH	A	50	2.276	-3.698	10.859	1.00	31.49	A
ATOM	2246	O	HOH	A	51	13.707	-1.745	14.947	1.00	26.81	A
ATOM	2247	O	HOH	A	52	-11.484	5.994	-4.734	1.00	28.94	A
ATOM	2248	O	HOH	A	53	15.597	8.025	12.778	1.00	25.87	A
ATOM	2249	O	HOH	A	54	-12.859	-0.373	-16.318	1.00	38.15	A
ATOM	2250	O	HOH	A	55	-21.136	-9.246	-1.882	1.00	23.94	A
ATOM	2251	O	HOH	A	56	10.996	16.960	15.947	1.00	36.67	A
ATOM	2252	O	HOH	A	57	-6.591	9.869	-9.281	1.00	26.49	A
ATOM	2253	O	HOH	A	58	13.911	-11.174	2.291	1.00	30.38	A
ATOM	2254	O	HOH	A	59	-9.562	-10.942	-10.916	1.00	27.88	A

ATOM	2255	O	HOH	A	60	4.745	-19.626	-5.080	1.00	29.55	A
ATOM	2256	O	HOH	A	61	-1.717	-8.359	-10.786	1.00	24.62	A
ATOM	2257	O	HOH	A	62	-10.559	-3.268	-13.949	1.00	24.21	A
ATOM	2258	O	HOH	A	63	-0.660	15.194	-5.517	1.00	22.53	A
ATOM	2259	O	HOH	A	64	9.037	-0.135	-9.783	1.00	36.19	A
ATOM	2260	O	HOH	A	65	-23.460	-16.827	8.631	1.00	29.91	A
ATOM	2261	O	HOH	A	66	-24.192	-1.276	5.295	1.00	27.96	A
ATOM	2262	O	HOH	A	67	-16.353	4.624	-11.962	1.00	32.05	A
ATOM	2263	O	HOH	A	68	-17.396	3.801	-9.450	1.00	28.58	A
ATOM	2264	O	HOH	A	69	10.752	-11.093	7.051	1.00	37.06	A
ATOM	2265	O	HOH	A	70	1.620	-15.965	-4.603	1.00	24.63	A
ATOM	2266	O	HOH	A	71	-8.238	12.427	-6.673	1.00	33.82	A
ATOM	2267	O	HOH	A	72	-16.577	-14.805	-9.290	1.00	29.62	A
ATOM	2268	O	HOH	A	73	9.083	-13.189	-4.221	1.00	35.45	A
ATOM	2269	O	HOH	A	74	10.287	7.919	-14.356	1.00	33.56	A
ATOM	2270	O	HOH	A	75	-20.538	-21.060	2.242	1.00	45.67	A
ATOM	2271	O	HOH	A	76	-1.640	14.388	9.613	1.00	30.93	A
ATOM	2272	O	HOH	A	77	40.049	-7.010	13.782	1.00	30.14	A
ATOM	2273	O	HOH	A	78	18.418	12.809	-8.404	1.00	37.11	A
ATOM	2274	O	HOH	A	79	-25.942	-2.805	-10.608	1.00	34.88	A
ATOM	2275	O	HOH	A	80	16.293	-4.489	17.257	1.00	25.34	A
ATOM	2276	O	HOH	A	81	-16.209	-8.340	11.406	1.00	40.96	A
ATOM	2277	O	HOH	A	82	11.439	19.084	12.127	1.00	33.82	A
ATOM	2278	O	HOH	A	83	20.159	2.221	5.570	1.00	28.54	A
ATOM	2279	O	HOH	A	84	-13.713	5.569	-10.421	1.00	29.53	A
ATOM	2280	O	HOH	A	85	-7.262	16.174	-0.684	1.00	29.54	A
ATOM	2281	O	HOH	A	86	9.742	-10.617	-7.415	1.00	25.62	A
ATOM	2282	O	HOH	A	87	-20.632	0.152	7.971	1.00	39.94	A
ATOM	2283	O	HOH	A	88	1.339	18.421	-9.397	1.00	43.65	A
ATOM	2284	O	HOH	A	89	-4.943	13.752	20.778	1.00	37.74	A
ATOM	2285	O	HOH	A	90	-3.157	10.534	20.505	1.00	40.33	A
ATOM	2286	O	HOH	A	91	20.471	14.004	-1.018	1.00	22.59	A
ATOM	2287	O	HOH	A	92	-3.126	-6.909	11.806	1.00	31.06	A
ATOM	2288	O	HOH	A	93	-14.587	-14.560	24.267	1.00	48.31	A
ATOM	2289	O	HOH	A	94	4.029	-14.349	32.347	1.00	56.74	A
ATOM	2290	O	HOH	A	95	7.949	-15.761	-2.076	1.00	40.76	A
ATOM	2291	O	HOH	A	96	-2.357	13.362	-6.866	1.00	25.37	A
ATOM	2292	O	HOH	A	97	0.273	12.223	-13.491	1.00	30.12	A
ATOM	2293	O	HOH	A	98	23.889	-3.917	11.357	1.00	25.67	A
ATOM	2294	O	HOH	A	99	-4.748	-9.020	-11.939	1.00	46.38	A
ATOM	2295	O	HOH	A	100	-1.430	-10.359	-13.316	1.00	31.41	A
ATOM	2296	O	HOH	A	101	-10.739	-23.422	-9.199	1.00	39.50	A
ATOM	2297	O	HOH	A	102	-3.937	14.980	-8.334	1.00	24.93	A
ATOM	2298	O	HOH	A	103	-7.054	-10.787	-10.296	1.00	33.68	A
ATOM	2299	O	HOH	A	104	13.492	0.660	13.579	1.00	31.04	A
ATOM	2300	O	HOH	A	105	-6.920	-14.447	-11.281	1.00	45.39	A
ATOM	2301	O	HOH	A	106	13.348	22.708	2.254	1.00	36.30	A
ATOM	2302	O	HOH	A	107	5.408	-11.711	-5.405	1.00	31.10	A
ATOM	2303	O	HOH	A	108	18.256	-2.341	15.534	1.00	28.95	A
ATOM	2304	O	HOH	A	109	-8.503	0.787	3.249	1.00	41.16	A
ATOM	2305	O	HOH	A	110	14.317	3.040	-11.205	1.00	42.00	A
ATOM	2306	O	HOH	A	111	11.881	17.271	-4.308	1.00	37.83	A
ATOM	2307	O	HOH	A	112	19.020	15.966	5.172	1.00	45.54	A
ATOM	2308	O	HOH	A	113	0.998	-12.806	-8.453	1.00	43.81	A
ATOM	2309	O	HOH	A	114	13.315	-10.545	8.002	1.00	33.76	A
ATOM	2310	O	HOH	A	115	-10.798	3.629	0.360	1.00	29.35	A
ATOM	2311	O	HOH	A	116	26.244	9.778	1.025	1.00	38.48	A
ATOM	2312	O	HOH	A	117	-18.933	-5.540	7.951	1.00	21.69	A
ATOM	2313	O	HOH	A	118	-2.346	9.089	14.123	1.00	28.55	A
ATOM	2314	O	HOH	A	119	12.331	-3.683	-6.285	1.00	28.50	A
ATOM	2315	O	HOH	A	120	17.652	7.204	6.269	1.00	33.34	A
ATOM	2316	O	HOH	A	121	-20.972	-5.394	10.153	1.00	29.22	A
ATOM	2317	O	HOH	A	122	1.126	-29.138	3.663	1.00	54.55	A
ATOM	2318	O	HOH	A	123	19.859	5.269	4.518	1.00	48.81	A

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ATOM   2319  O   HOH A 124      16.235  -4.760  13.356  1.00 24.74      A
ATOM   2320  O   HOH A 125      -1.781  27.895  -1.429  1.00 49.94      A
ATOM   2321  O   HOH A 126       0.978   3.103 -14.170  1.00 33.01      A
ATOM   2322  O   HOH A 127      23.932   8.429 -15.415  1.00 43.20      A
ATOM   2323  O   HOH A 128     -15.975  -7.260  14.283  1.00 35.46      A
ATOM   2324  O   HOH A 129      -5.663 -12.681   1.284  1.00 25.44      A
ATOM   2325  O   HOH A 130      -9.888 -12.927   7.395  1.00 35.96      A
ATOM   2326  O   HOH A 131      25.472   3.261  -1.345  1.00 31.42      A
ATOM   2327  O   HOH A 132       0.225  -4.710   9.057  1.00 40.52      A
ATOM   2328  O   HOH A 133       1.153  -8.592 -10.392  1.00 41.49      A
ATOM   2329  O   HOH A 134       0.318  -2.638 -15.320  1.00 36.09      A
ATOM   2330  O   HOH A 135      -6.483  17.186  -5.700  1.00 31.77      A
ATOM   2331  O   HOH A 136     -11.747   5.541  -2.116  1.00 37.63      A
ATOM   2332  O   HOH A 137       3.033   5.741 -16.256  1.00 60.91      A
ATOM   2333  O   HOH A 138      15.857  -9.756   3.393  1.00 42.40      A
ATOM   2334  O   HOH A 139       1.315  24.812   0.302  1.00 37.92      A
ATOM   2335  O   HOH A 140      18.429  -8.563   6.665  1.00 40.06      A
ATOM   2336  O   HOH A 141       8.361  17.182  -5.869  1.00 35.77      A
ATOM   2337  O   HOH A 142      -3.830  -1.160   8.545  1.00 30.75      A
ATOM   2338  O   HOH A 143     -11.080  -0.626 -21.190  1.00 42.20      A
ATOM   2339  O   HOH A 144     -25.620  -5.418 -10.124  1.00 24.22      A
ATOM   2340  N9  ANE A 400      -0.759 -10.830   5.271  1.00 36.71      A
ATOM   2341  C8  ANE A 400      -1.712 -10.252   4.469  1.00 37.40      A
ATOM   2342  N7  ANE A 400      -1.529 -10.440   3.198  1.00 37.33      A
ATOM   2343  C5  ANE A 400      -0.400 -11.181   3.134  1.00 37.65      A
ATOM   2344  C6  ANE A 400       0.318 -11.704   2.059  1.00 38.63      A
ATOM   2345  N6  ANE A 400      -0.086 -11.507   0.797  1.00 39.54      A
ATOM   2346  N1  ANE A 400       1.443 -12.423   2.375  1.00 37.38      A
ATOM   2347  C2  ANE A 400       1.792 -12.580   3.654  1.00 38.46      A
ATOM   2348  N3  ANE A 400       1.207 -12.139   4.749  1.00 39.20      A
ATOM   2349  C4  ANE A 400       0.099 -11.435   4.400  1.00 37.67      A
END
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CLAIMS

1. An isolated binding pocket of a receptor tyrosine kinase (RTK) that regulates the kinase domain of the receptor tyrosine kinase.
2. An isolated binding pocket as claimed in claim 1 wherein the RTK is an Eph receptor, preferably an EphB2 receptor.
3. Molecules or molecular complexes that comprise all or parts of either one or more of a binding pocket as claimed in claim 1 or 2, or a homolog of the binding pocket that has similar structure and shape.
4. A crystal comprising a binding pocket of an RTK that regulates the kinase domain of the RTK.
5. A crystal as claimed in claim 4 wherein the binding pocket is in an autoinhibited state.
6. A crystal comprising a juxtamembrane region and/or kinase domain of an RTK, or part thereof.
7. A crystal formed by a juxtamembrane region and a kinase domain of an RTK in an autoinhibited state.
8. A crystal comprising a binding pocket of an RTK that regulates the kinase domain of the RTK, in association with a ligand.
9. A crystal comprising a binding pocket of an RTK as claimed in claim 1 or 2 complexed or associated with a ligand.
10. A crystal as claimed in claim 9 wherein the ligand is a nucleotide or analogue thereof, a substrate or analogue thereof, a cofactor, and/or heavy metal atom.
11. A crystal as claimed in claim 9 wherein the ligand is a modulator of the activity of an RTK
12. A crystal as claimed in any of the preceding claims wherein the shape and structure of the binding pocket is defined by one or more atomic interactions or enzyme atomic contacts in Table 2.
13. A crystal comprising a binding pocket of an Eph receptor.
14. A crystal comprising a binding pocket of an Eph receptor and a nucleotide or analogue thereof, from which it is possible to derive structural data for the nucleotide.
15. A crystal according to any preceding claim wherein the Eph receptor is derivable from a human cell.
16. A crystal according to any preceding claim, wherein the an Eph receptor is EphB2.
17. A crystal according to any preceding claim wherein the crystal comprises a binding pocket of an Eph receptor having a mutation in the part of the enzyme which is involved in phosphorylation.
18. A crystal according to any preceding claim wherein the crystal comprises a binding pocket of an Eph receptor having a mutation in one or more tyrosine residues.
19. A crystal according to any preceding claim wherein the binding pocket is in association with a cofactor.
20. A crystal according to any preceding claim having the structural coordinates shown in Table 3.
21. A model of a binding pocket of an RTK made using a crystal according to any preceding claim.
22. A model of: (a) a binding pocket of an RTK that is involved in maintaining an autoinhibited state or active state of an RTK or regulates the kinase domain of an RTK; and (b) a modification of the model of (a).

23. A model of a binding pocket of the present invention that substantially represents the structural coordinates specified in Table 3

24. A computer-readable medium having stored thereon a crystal or model according to any of the preceding claims.

25. A method of determining the secondary and/or tertiary structures of a polypeptide comprising the step of using a crystal or model according to any of the preceding claims.

26. A method of screening for a ligand capable of associating with a binding pocket and/or inhibiting or enhancing the atomic contacts of interactions in a binding pocket, comprising the use of a crystal or model according to any of the preceding claims.

27. A ligand identified by a method according to claim 26.

28. A ligand identified by a method according to claim 26 that is a modulator capable of modulating the activity of the RTK.

29. A method of identifying a modulator of an RTK comprising determining if a test agent inhibits or potentiates an autoinhibited state or active state of a kinase domain of the RTK.

30. A method as claimed in claim 29 comprising one or more of the following additional steps:

(a) testing whether the modulator is a modulator of the activity of a RTK, preferably testing the activity of the modulator in cellular assays and animal model assays;

(b) modifying the modulator;

(c) optionally rerunning steps (a) or (b); and

(d) preparing a pharmaceutical composition comprising the modulator.

31. A method of conducting a drug discovery business comprising:

(a) providing one or more systems employing the atomic interactions, atomic contacts, or structural coordinates of a binding pocket of an RTK, for identifying agents by their ability to inhibit or potentiate the atomic interactions or atomic contacts of a binding pocket; and

(b) conducting therapeutic profiling of agents identified in step (a), or further analogs thereof, for efficacy and toxicity in animals; and

(d) formulating a pharmaceutical preparation including one or more agents identified in step (b) as having an acceptable therapeutic profile.

32. A method of conducting a drug discovery business comprising:

(a) providing one or more systems for identifying agents by their ability to inhibit or potentiate an autoinhibited state or active state of a kinase domain of an RTK; and

(b) conducting therapeutic profiling of agents identified in step (a), or further analogs thereof, for efficacy and toxicity in animals; and

(c) formulating a pharmaceutical preparation including one or more agents identified in step (b). as having an acceptable therapeutic profile.

33. A method of conducting a target discovery business comprising:

(a) providing one or more systems employing the atomic interactions, atomic contacts, or structural coordinates of a binding pocket of an RTK, for identifying agents by their ability to

inhibit or potentiate the atomic interactions or atomic contacts, or providing one or more systems for identifying agents by their ability to inhibit or potentiate an autoinhibited state or active state of a kinase domain of an RTK;

(b) optionally conducting therapeutic profiling of agents identified in step (a) for efficacy and toxicity in animals; and

(c) licensing, to a third party, the rights for further drug development and/or sales for agents identified in step (a), or analogs thereof.

34. A method for regulating the kinase domain of an RTK by changing a binding domain or pocket of a RTK that regulates the kinase domain, from an autoinhibited state to an active state or from an active state to an autoinhibited state

35. A method for inhibiting kinase activity of an RTK comprising maintaining the RTK or a binding pocket thereof involved in regulating the kinase domain in an autoinhibited state, or potentiating an autoinhibited state for the RTK or binding pocket thereof involved in regulating the kinase domain.

36. Use of a modulator according to any preceding claim in the manufacture of a medicament to treat and/or prevent a disease in a mammalian patient.

37. A pharmaceutical composition comprising a ligand or modulator according to any preceding claim, and optionally a pharmaceutically acceptable carrier, diluent, excipient or adjuvant or any combination thereof.

38. A method of treating and/or preventing a disease comprising administering a ligand, modulator, or pharmaceutical composition according to any preceding claim to a mammalian patient.

39. A method of treating or preventing a condition or disease associated with an RTK in a cellular organism, comprising:

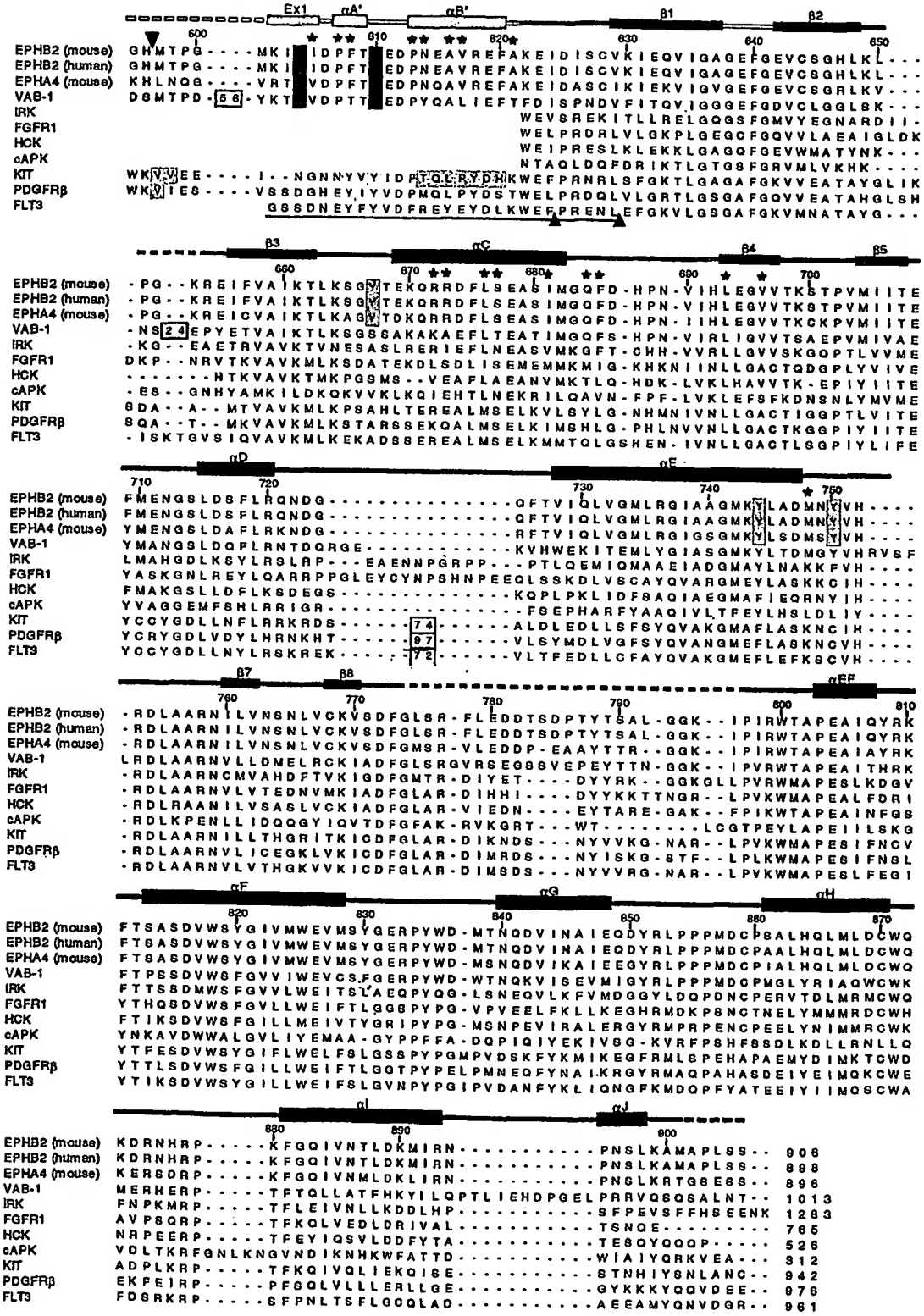
(a) administering a pharmaceutical composition as claimed in claim 38; and

(b) activating or inhibiting the RTK to treat or prevent the disease.

40. A method for treating or preventing a condition or disease involving increased RTK activity comprising maintaining the RTK, or a binding pocket thereof involved in regulating the kinase domain of the RTK, in an autoinhibited state

41. A crystal comprising an RTK binding pocket, substantially as described herein and with reference to the accompanying figures.

Figure 1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β2
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FGFR1
HCK
cAPK
KIT
PDGFRβ
FLT3
β3
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β5
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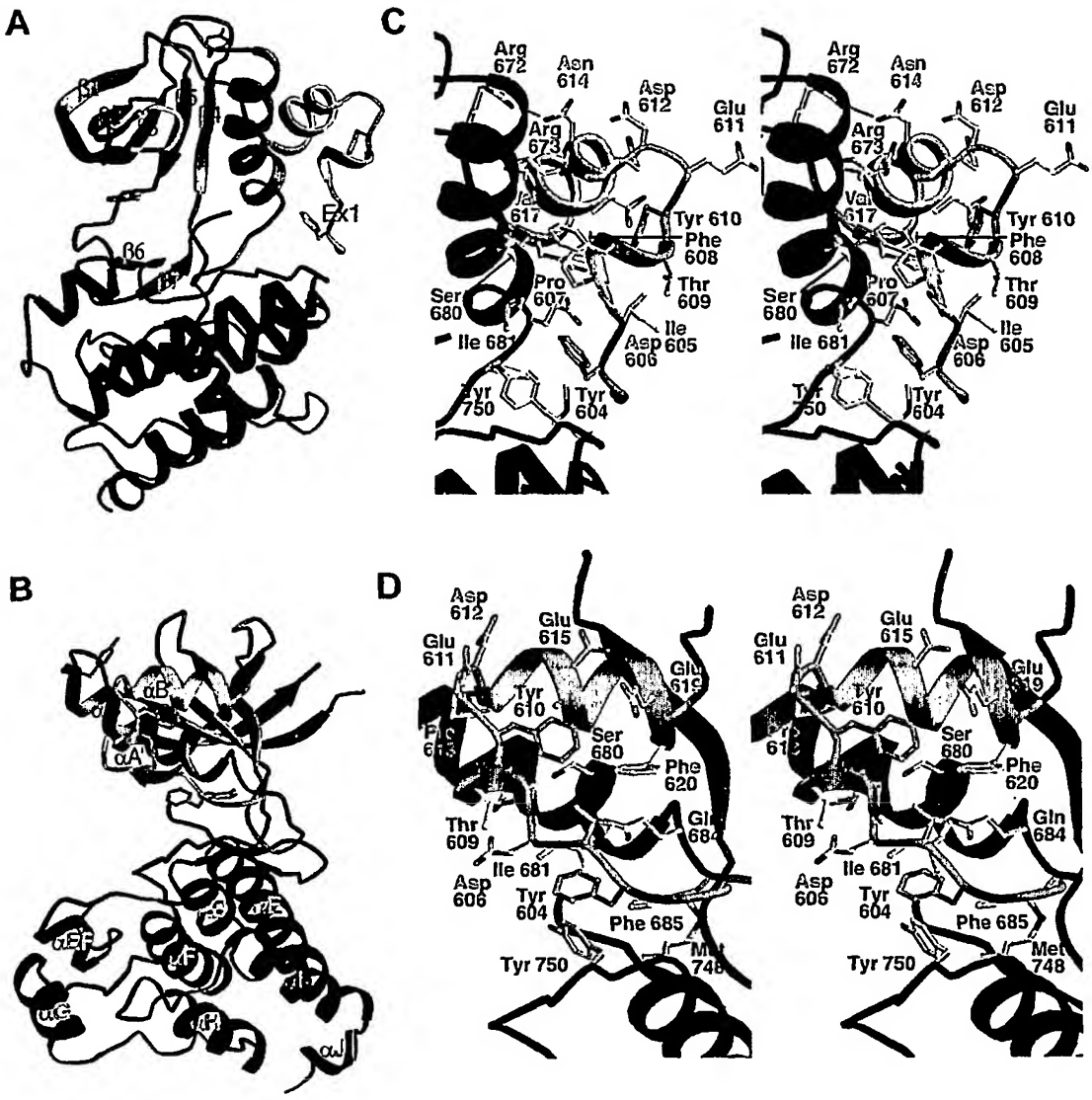
β7
β8
αEF
αF
αG
αH
αI
αJ

Figure 2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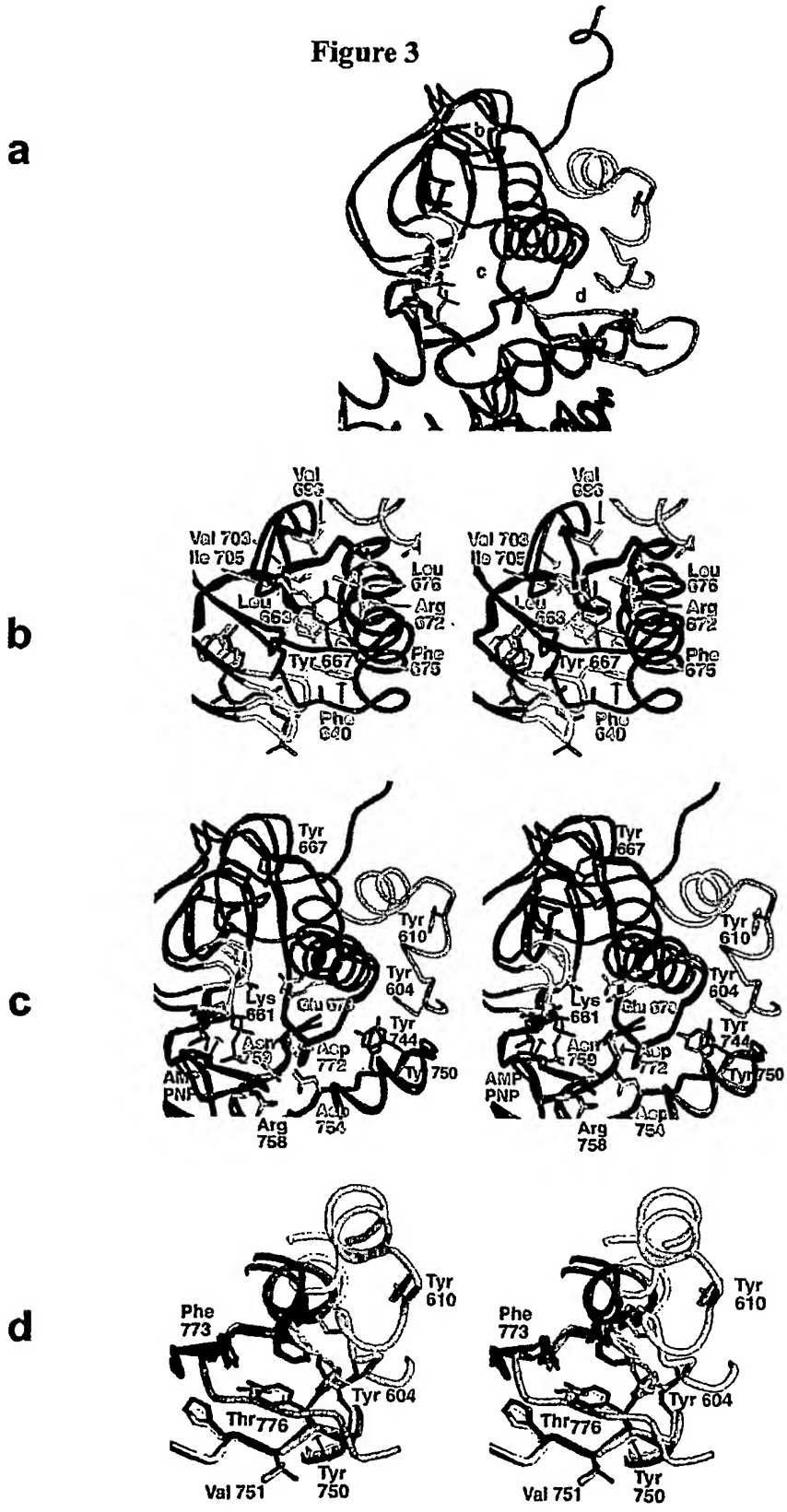
Phe 685
Met 748

Figure 3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Lys 661
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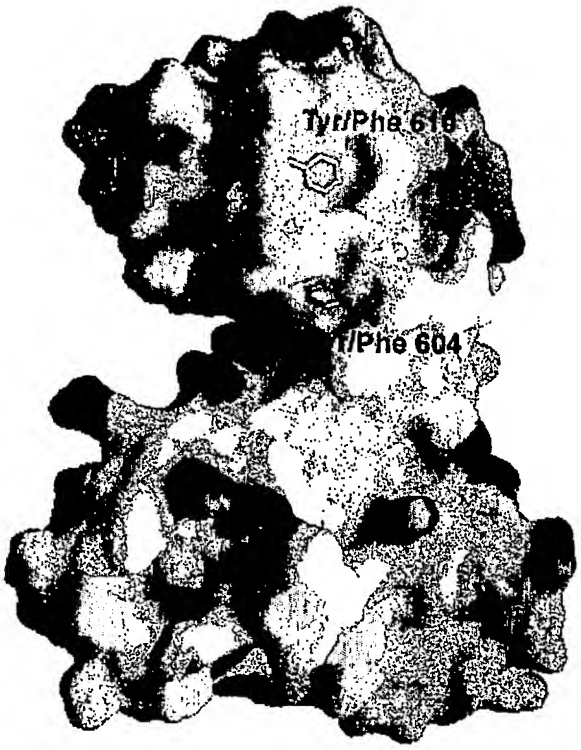
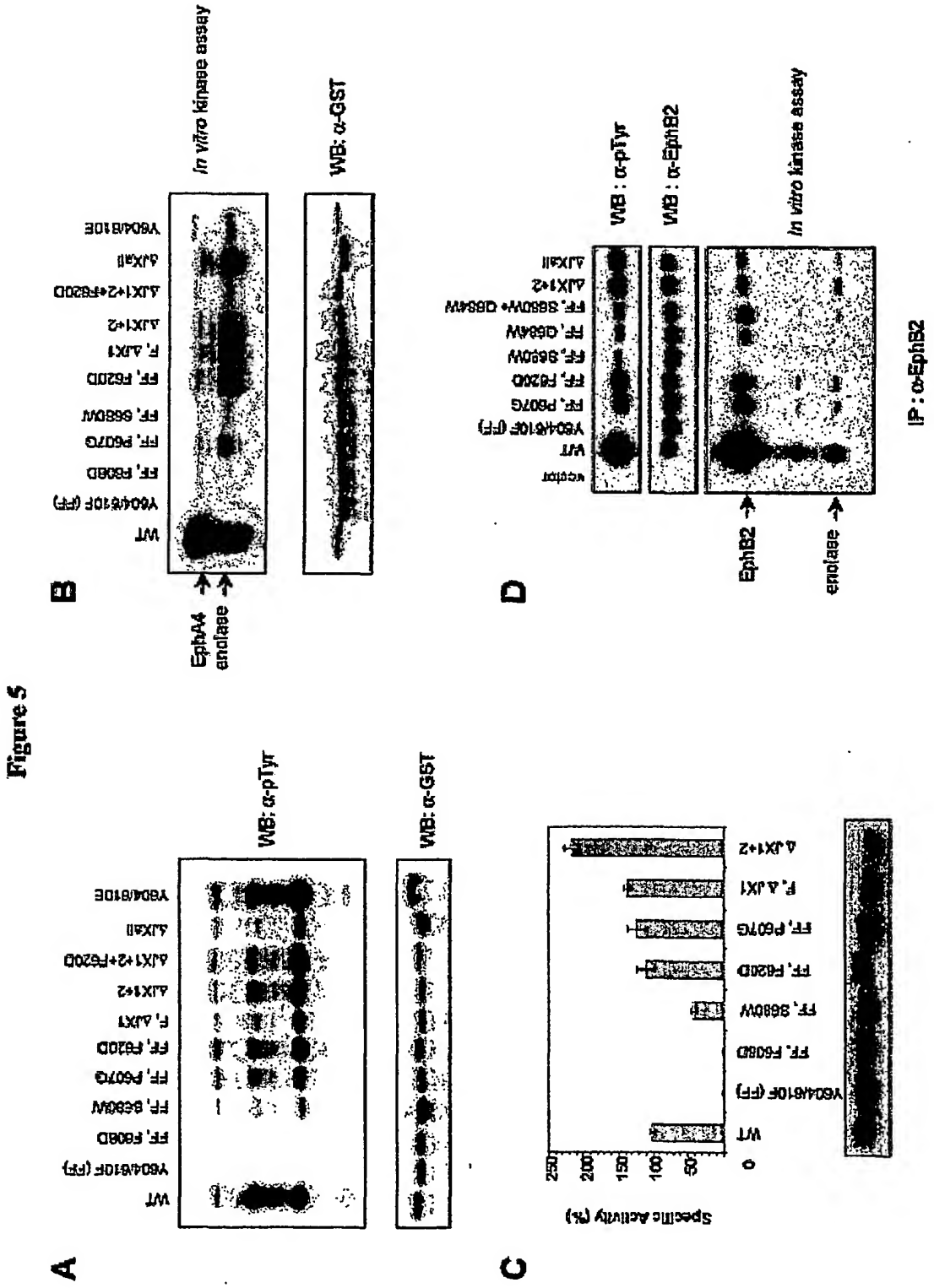
Val 751

Figure 4

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WB: α-GST
WT
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FF, S680W
FF, P607G
FF, F620D
F, ΔJX1
ΔJX1+2
ΔJX1+2+F620D
ΔJX3II
V604/610E
B
In vitro kinase assay
WB: α-GST
EphA4
enolase
WT
V604/610E (FF)
FF, F608D
FF, P607G
FF, S680W
FF, F620D
F, ΔJX1
ΔJX1+2
ΔJX1+2+F620D
ΔJX3II
V604/610E
C
Specific activity (%)
250
200
150
100
50
0
WT
V604/610E (FF)
FF, F608D
FF, S680W
FF, F620D
FF, P607G
F, ΔJX1
ΔJX1+2
D
WB : α-pTyr
WB : α-EphB2
In vitro kinase assay
IP : α-EphB2
vector
WT
V604/610E (FF)
FF, P607G
FF, F620D
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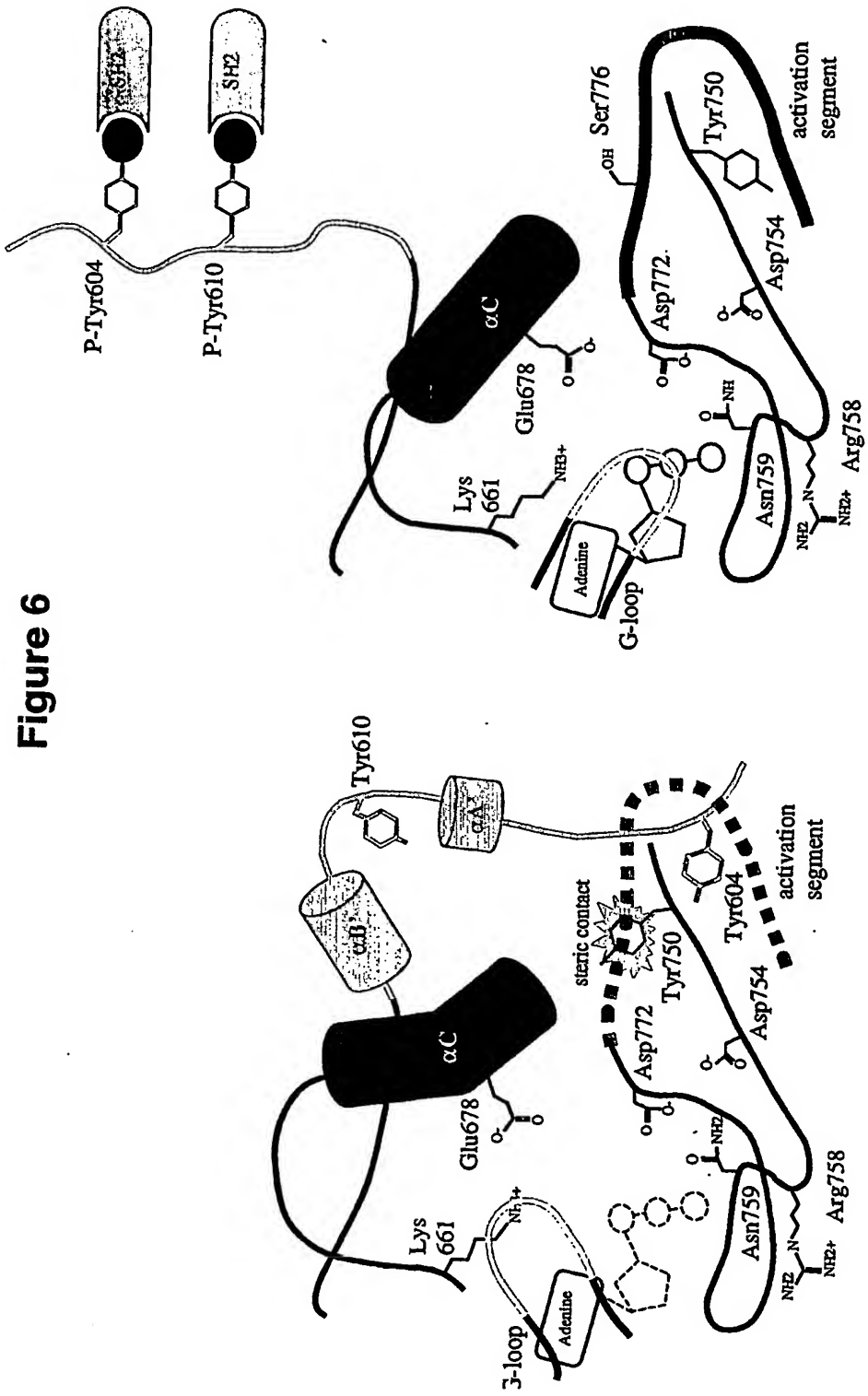
FF, S680W+ Q684W
ΔJX1+2
ΔJX3II
EphB2
enolase

Figure 5

Figure 6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Arg758
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αA'
αD'
steric contact
Tyr604
Unphosphorylated, autoinhibited EphB2